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MODERN CLINICAL MEDICINE

INFECTIOUS DISEASES

EDITED BY

J. C. WILSON, A.M., M.D.

PROFESSOR OF MEDICINE IN THE JEFFERSON MEDICAL COLLEGE; PHYSICIAN-IN-CHIEF
TO THE GERMAN HOSPITAL, PHILADELPHIA; PHYSICIAN TO THE
JEFFERSON AND PENNSYLVANIA HOSPITALS, ETC.

AN AUTHORIZED TRANSLATION FROM "DIE DEUTSCHE KLINIK"
UNDER THE GENERAL EDITORIAL SUPERVISION OF

JULIUS L. SALINGER, M.D.

*WITH TWO COLORED PLATES AND
SIXTY ILLUSTRATIONS IN THE TEXT*



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INTRODUCTION

THE beginning of the nineteenth century found the German-speaking profession the leaders in clinical medicine. At that period the great schools of Vienna and Berlin vied with each other for the supremacy in original research and clinical experience. This once-gained supremacy the Germans have never yielded, for, at the beginning of the twentieth century, the teachings of German clinicians are found in the van. They were the ones who first used and developed the term and meaning of "internal medicine." It is then not too much to claim that a work which shows the advanced thought of the best of German clinicians in the twentieth century may well be accepted as the standard of medical knowledge at this time. Clinical medicine to-day may be likened to a cluster ring, the individual gems of which have been dug from the deepest and most obscure mines of knowledge, and have been gathered in a general setting which to-day represents "internal medicine."

Professors Leyden and Klemperer have been exceedingly fortunate in the *Deutsche Klinik* in gathering the views of the most eminent German clinicians of the present day. To mention their names would be to designate specialists in distinct realms of medical science. It may be claimed of every article that it is thoroughly modern. This has, however, not been attained by rejecting what is old and true, and by admitting what is new and still untried. Theories have been largely discarded, and only such have been mentioned as form likely hypotheses in the explanation of morbid conditions of which we have as yet but a glimmer of the dawn, which with advancing knowledge will soon become the bright light of scientific certainty. It has been the attempt of the authors to render their articles eminently practical, and it may well be claimed that each one contains not only what is necessary for the obscure practitioner but also what is required by the teacher in medicine.

In preparing this volume on the Infectious Diseases, "flowered with the blossoms of learning and observation," it has been deemed expedient and as serving a most useful purpose to select from the entire work in the original all diseases which are now recognized as infections, and to combine them in

one general volume. This arrangement differs somewhat from the German. It was found necessary to add a few infectious diseases that were omitted in the original, such as Vaccinia, Varicella, Dengue, Yellow Fever, Weil's Disease, and Malta Fever. These have been written by the editors, so that a complete work on infectious diseases might be presented to the English-speaking medical profession. Syphilis and Leprosy will be thoroughly considered in the volume on Dermatology. As far as possible the style of the individual authors has been retained. It is our earnest hope that the new English version may fill as important a place as has the original, which has become the standard in clinical medicine.

JULIUS L. SALINGER.

1729 NORTH 42ND STREET, PHILADELPHIA.

EDITOR'S PREFACE

THE publication of the *Deutsche Klinik* at the beginning of the twentieth century corresponds to an epoch not only in the progress of time but also in the history of medicine. Time, as one of the editors of this great work has well said, moves on without regard to arbitrary divisions such as days, years or centuries and its progress is not measured by milestones. Human knowledge advances in the same way. If there appear from time to time to be sudden bursts of improvement they will be found upon careful study of the facts to be the manifestations of previous forces acting quietly and progressively, just as the orderly succession of the seasons is the result of unnoted but irresistible and continuously acting cosmic energy. Long periods of patient research precede the great discoveries in medicine and broad generalizations rest upon many carefully studied facts. The great events of medical history by which we mark its general progress bear a sort of analogy to the divisions by which we chronicle the passing of the ages. They are the dates of knowledge.

The later years of the nineteenth and the opening of the twentieth century constitute one of the most brilliant and impressive of these epochs. To celebrate it important scientific publications, especially in medicine, have been issued in several languages. It is no disparagement of others to say that the *Deutsche Klinik*, the sum of the collective labor of the Master Minds of Medicine in Germany, stands, as a summary of existing knowledge and as a permanent record of the medical science of our times, in the foremost rank.

Those to whom this work is known in the original will welcome it in its English garb and convenient arrangement. Those to whom it first comes in the translation will find it not only the literary embodiment of the most advanced science but also in a surprising degree adapted to the everyday needs of the practitioner, the student and the teacher.

This statement is especially true of the present volume. The Infectious Diseases have recently yielded unlooked for and most significant results to the genius of patient research. Bacteriology and the laboratory investigations

of the sera of man and animals in health and disease have cleared up many obscure points in our knowledge of the infections and hold out the fair promise of many additional and most important facts. Our knowledge of the natural history of this great group of maladies, of their management and above all of their prophylaxis, has been to a great extent revolutionized. The record of what has been accomplished and the lines of research along which further work is to be done have been indicated by many of the contributors to this volume in their proper and suggestive relationship with the descriptions of those aspects of disease which to some may appear of more immediate practical interest. It is fitting that this volume should be the first of the series and the writer deems himself fortunate in having been selected to share the labor of preparing it for the press.

The Translator has added greatly to the usefulness of the work by abandoning the arrangement in the form of lectures, while retaining the personal style which lends attractiveness to the lecture and by collecting associated subjects together in separate volumes. No attempt has been made to modify Professor Salinger's terse and idiomatic rendering into English. Even where here and there the literal translation has seemed to involve some sacrifice of style, comparison with the original has fully vindicated the judgment of the Translator.

J. C. WILSON.

1509 WALNUT STREET, PHILADELPHIA.

LIST OF CONTRIBUTIONS

Enteric or Typhoid Fever:

I. Etiology of Enteric Fever. By F. KLEMPERER, Berlin.

II. Diagnosis and Prognosis of Enteric Fever. By C. LIEBERMEISTER, Tübingen.

III. Treatment of Enteric Fever. By F. KLEMPERER, Berlin.

Paratyphoid. By Dr. ALBERT BRION, Strassburg.

Typhus Fever and Relapsing Fever. By L. LICHTHEIM, Königsberg.

Dengue. By J. C. WILSON, Philadelphia.

Yellow Fever. By JULIUS L. SALINGER, Philadelphia.

Influenza. By P. FÜRBRINGER, Berlin.

Influenza Since the Last Pandemic. By N. ORTNER, Vienna.

Malarial Diseases. By F. LÖFFLER, Greifswald.

Measles, Morbilli, Rubeola. By O. HEUBNER, Berlin.

Rötheln, Rubella, German Measles. By CH. BÄUMLER, Freiburg.

Scarlet Fever, Scarlatina. By O. HEUBNER, Berlin.

Smallpox, Variola. By CH. BÄUMLER, Freiburg.

Vaccinia, Cowpox, Kinpox. By J. C. WILSON, Philadelphia.

Vaccination. By J. C. WILSON, Philadelphia.

Varicella, Chickenpox. By J. C. WILSON, Philadelphia.

Erysipelas. By A. SCHÜTZE, Berlin.

Epidemic Cerebrospinal Meningitis. By H. EICHHORST, Berlin.

Diphtheria and Diphtheritic Croup. By A. BAGINSKY, Berlin.

Pneumonia. By E. v. LEYDEN, Berlin.

Tuberculosis as an Acute Infectious Disease (Acute Miliary Tuberculosis, Acute Tuberculosis of the Serous Membranes, Acute Caseous Pneumonia). By G. CORNET, Berlin.

Acute Articular Rheumatism. By CH. BÄUMLER, Freiburg.

Sepsis. By TH. v. JÜRGENSEN, Tübingen.

- Dysentery and Ameba Enteritis.* By G. HOPPE-SEYLER, Kiel.
- Cholera Nostras and Cholera Indica.* By TH. RUMPF, Hamburg.
- The Plague, the Bubonic Plague, and the Pest.* By W. KOLLE, Berlin.
- Epidemic Parotitis, Mumps.* By H. FALKENHEIM, Königsberg.
- Pertussis, Whooping-Cough, Tussis-Convulsiva.* By A. BAGINSKY, Berlin.
- Angina (Tonsillitis) as an Infectious Disease.* By M. MOSSE, Berlin.
- Malta Fever.* By JULIUS L. SALINGER, Philadelphia.
- Weil's Disease, Icterus Infectiosus, Acute Febrile Icterus.* By J. C. WILSON, Philadelphia.
- Tetanus.* By P. JACOB, Berlin.
- Hydrophobia, Rabies.* By F. PENZOLDT, Erlangen.
- Anthrax.* By A. NICOLAIER, Berlin.
- Glanders, Farcy.* By A. NICOLAIER, Berlin.
- Foot and Mouth Disease.* By A. NICOLAIER, Berlin.
- Actinomycosis.* By A. NICOLAIER, Berlin.
- Immuno-Therapy.* By JOSEPH MCFARLAND, Philadelphia.

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ENTERIC OR TYPHOID FEVER

I. ETIOLOGY OF ENTERIC FEVER

By F. KLEMPERER, BERLIN

Etiology.—For some time previous to the bacteriologic era, opinions had been formed regarding the etiology of enteric fever, which approached very closely to our present views. For a long time afterwards the affection was attributed to processes of stagnation and decomposition which were combined with vague views regarding changes in the ground and air, with decomposition of food products, etc. The English clinician Budd¹ about the middle of the last century promulgated the view that the enteric fever patient was in direct etiologic relation with the typhoid poison contained in his evacuations. The typhoid poison arises in the body of the sick and is discharged in its fecal contents; it is not a product of decomposition of the fecal material, but a specific agent; the smallest quantity of the typhoid stool is sufficient to propagate the disease, which never arises spontaneously, but in each case is in direct relation with the previous one—all these thoughts Budd announced clearly and distinctly and even expressed the opinion that by a process which would render the enteric stools innocuous the distribution of the disease might be prevented.

Budd's opinions were forced to the rear by the well-known ground-water theory of Pettenkofer, which dominated the third quarter of the last century. This theory depended upon the observation of Buhl which was published in 1865, that in Munich the mortality from enteric fever was in a certain ratio to the height of the ground-water, that upon a low condition of the ground-water the mortality increased. According to Pettenkofer's views, the typhoid poison required, as he also looked upon it as something specific, a maturing process in the ground, from whence it was carried through the air, more frequently through the water, into the human organism; the exit of the poison from the earth was hindered, or at least made very difficult by the high condition of the ground-water, whereas dry weather and a low stand of the ground-water favored the exhalation of the virus.

The rapid rise of bacteriology, due to Koch's discoveries in the last quarter of the previous century, caused Pettenkofer's theory to be discredited and Budd's views were again brought forward. The specific agent of enteric fever was recognized in the TYPHOID BACILLUS discovered by Gaffky in 1884, and it was determined that this agent did not require an alteration or maturing process in the earth, but that it found its exit from the body in the feces of

¹ Lancet, p. 156, 1859 and 1860.

the sick, ripe and ready to infect other individuals. The study of the bacillus, its morphology and biology, its distribution inside and outside of the body, has shed light regarding numerous points which previously were necessarily dark, so that to-day we have almost a complete picture of the etiology and pathogenesis of enteric fever. Before entering upon the same I shall briefly relate the most important bacteriological data; I shall follow the exposition which I have given in my "Grundriss der klinischen Bakteriologie," which I have published conjointly with E. Levy in Strassburg.¹

THE TYPHOID BACILLI

Morphology of the Typhoid Bacilli.—The bacilli of enteric fever, first described by R. Koch and Eberth, and first cultivated in pure culture by Gaffky in 1884, are short, plump rods with rounded ends ($0.5-20.9:1-3\ \mu$); in the tissues they are usually found isolated; in cultures, on the other hand, they are found in pairs, and not infrequently in long chains (threads). They contain from 8 to 18 terminal and lateral flagellæ (which can only be seen by special staining methods—Löffler's flagella stain), and in consequence show extraordinary motility, with a snake-like movement. Their tinctorial property is somewhat less than that of other bacteria; they stain with difficulty; it is, therefore, advisable in staining, in using watery solutions, and also diluted carbofuchsin solution, to apply gentle heat. They do not stain according to Gram.

The typhoid bacillus does not appear to form spores. Gaffky found terminal, pale, egg-shaped bodies which did not stain, that he believed to be spores; these structures (pole-granules), upon further study, are to be looked upon as involution forms. Certainly these bacilli, which are the carriers of such bodies, are not distinguished by a special property of resistance; after heating for ten minutes, at a temperature of 60°C ., they are completely destroyed.

The most favorable temperature for the cultivation of the typhoid bacillus is 37°C .; it will, however, also flourish at the temperature of the room, the maximum temperature being 46°C .

The typhoid bacillus exists without the presence of oxygen, but not as well, by far, as in the presence of oxygen (facultative anærobiosis).

Typhoid Bacilli in Cultures.—The typhoid bacillus shows—in contrast to most of the other pathogenic bacteria—an opulent growth upon feebly acid culture media.

Gelatin Plate Culture. Deep colonies: Small, punctiform, sharply demarcated; with a low power, of a brownish-yellow color, and a whetstone contour. Superficial colonies: Much larger, forming a bluish, iridescent, fine coating, with irregular, saggy margins. Only the centre of the colony, with low magnification, shows a yellowish color; towards the border, a delicate furrowed linear net may be observed, so that here a leaf-like marking occurs. The gelatin is not liquefied.

Gelatin Stab Culture: Development of a grayish-white thread along the entire course of inoculation; the superficial growth again most developed, which has identically the same appearance as the superficial colonies upon the plate culture.

Gelatin Stroke Cultures: Beginning at the centre the surface of the gelatin soon develops a fine, iridescent, bluish covering.

Upon all gelatin cultures very frequently a peculiar milky turbidity of the culture media soon develops in the surroundings of the culture.

Agar Stroke Culture and Blood Serum: A white, not especially thick, coating without characteristic properties.

The condition upon potato culture is important: The typhoid bacilli grow as an invisible sod. It appears as though nothing had grown upon the surface of the potato; if, however, an attempt is made to scrape off some of the material with a platinum needle, it is soon noticed that a transparent, delicate veil covers the entire potato, and the microscopic examination reveals enormous masses of very actively motile rods.

¹ A. Hirschwald, Berlin, second edition, 1898, p. 160, etc.

This condition is entirely peculiar and appears to belong exclusively to typhoid bacilli. It is, however, not constant. There are potatoes upon which the bacilli of enteric fever develop into yellowish or brownish raised and sharply demarcated sods, and these potatoes show upon their surface a neutral or even alkaline reaction. The visible growth may also be artificially obtained in that the surface of inoculation on the potato is rendered alkaline. The typical, characteristic growth, however, only appears provided the potato, which appears to be the rule, possesses an acid reaction.

In milk the typhoid bacillus produces a feeble acid reaction, never coagulating; bouillon is uniformly rendered turbid; upon culture media containing grape sugar, milk sugar, or cane sugar, the typhoid bacillus does not give rise to fermentation. In peptone salt solution no indol is formed.

Life Properties of the Typhoid Bacilli.—The typhoid bacillus is characterized by remarkable resistance. In sterilized water it retains life for some time (up to three months) and even shows, at least at first, a slight increase. In other water, that is not sterilized, it perishes in about fourteen days on account of the presence of water bacteria. It is encroached upon by these water bacteria, this occurring more rapidly in flowing water than in still water. Under favorable circumstances, protected from light, drying and from other bacteria, the typhoid bacilli retain their property of life for a very long time; so in milk, that has been experimentally contaminated, for thirty-five days bacilli which were living and showed properties of development were grown; in mud taken from rivers and wells this condition was noted after three weeks. Buried in superficial layers of earth, they have been shown to be alive after five and one-half months. Dried in thin layers of earth, they remain alive from twenty to thirty days; dried upon various articles of clothing, for two to three months (Uffelmann). They remain for a long time in the feces, three months at the longest, provided, however, that there are not present simultaneously many bacteria which produce decomposition. In the dead body they also appear to retain their activity for a long time (Lösener). They bear cold well; alternate freezing and thawing does not injure them. They are less resistant to heat, as has been previously mentioned. Carbolic acid in proportion to one quarter per cent. to the culture solutions does not inhibit the development of a colony.

Animal Pathogenicity and Toxins of the Typhoid Bacilli.—Mice, guinea-pigs, rabbits, goats, etc., perish after inoculation of virulent typhoid bacilli (freshly cultivated from the spleen of a typhoid case), showing a fall in temperature, spasms and diarrhea. In a subcutaneous injection relatively large quantities of bacilli are necessary, less being required for an intraperitoneal or intravenous injection. The fatal effect is particularly due to an intoxication which is produced. With the filtrate of the bouillon culture, which is free from germs and with dead typhoid bacilli, the previously mentioned animals may be killed, giving rise to the same phenomena. With markedly virulent bacilli these animals, but especially white mice, may be killed in an intraperitoneal injection with so small a number of bacteria, and post mortem the bacillus will be found in such large quantities in the blood that an increase of the micro-organism in the animal body is beyond all doubt. Therefore, the typhoid bacillus disease of animals cannot entirely be denied as being of the character of an actual infection. Naturally, this infection does not clinically conform to enteric fever in man. It must, however, be observed that in nature actual typhoid disease does not exist in animals. The attempt to produce true typhoid (or only a typhoid bacillus intoxication) in animals by the introduction of bacteria per os meets with great difficulties. After rendering the contents of the stomach alkaline and keeping the bowels at rest by opium, in this manner, in guinea-pigs, alterations were produced in the bowel, in the mesenteric glands, spleen, etc., which resembled the changes in human typhoid. Complete, positive animal experiments, with the pathologico-anatomical findings of true enteric fever, are not recorded in literature.

The pyogenic action of the typhoid bacillus can easily be demonstrated by experiment. Abscesses frequently form at the point of injection. Upon a decreased virulence of the bacteria only a local pus-formation occurs; fatal intoxication does not take place.

In the filtrate of the typhoid bouillon cultures Brieger and Fränkel demonstrated a toxin which they believed to belong to the toxalbumins. More important is the toxin contained in the typhoid bacilli (protein toxin) which R. Pfeiffer produced by killing young agar cultures by chloroform vapor or heating the culture for one hour at 54° C.; 8 to 10 milligrams of the dead bacteria are sufficient to kill a guinea-pig.

To properly appreciate the etiological connection of the previously described typhoid bacilli in man, we must next inquire AS TO THE OCCURRENCE OF THE BACILLUS IN ENTERIC FEVER PATIENTS. A most important fact is the regular finding of typhoid bacilli in Peyer's patches, the mesenteric glands and in the spleen. Their demonstration in the intestinal wall and in the glands is naturally only possible at the autopsy; in the spleen, however, the bacilli have been demonstrated upon numerous occasions by puncture intravital. According to the unanimous opinion of numerous investigators, it may be maintained with certainty that the occurrence of bacilli in the intestinal walls, in the lymph glands belonging to the intestine, and in the spleen is a constant and unexceptional condition in all cases of enteric fever. In other abdominal organs also, for example, the liver, further in the bone marrow, the typhoid bacillus has been demonstrated in individuals having perished from typhoid fever. In the tissues the bacilli are always collected in clumps, which occasionally show a connection with vessels. This also proves the distribution of the bacilli by the blood current. In the circulating blood of the enteric fever patient the demonstration of the bacilli has also been possible—for example, in the blood of the veins, after blood has been removed by a syringe—but this appears to be exceptional. As a rule, the blood of the patient during life is sterile, the important road of transport of the bacilli appears to be by the lymph system. In the roseolar eruption the bacilli have been repeatedly demonstrated by the withdrawal of a few drops of blood and cultivation. The bacilli were first shown to be present by Neuhaus, ¹ later by Rüttimeyer, Thiemich and others, in a microscopic section by E. Fränkel. The bacilli, however, appear to be only rarely present in the eruption; many authors did not succeed in finding them (Gaffky, Janowski, and others). Neufeld ² showed, however, that the bacteria were regularly present in the fluid of the roseolar eruption—he found them 13 times in 14 cases—but for cultivation it is necessary that the blood taken from the roseolar eruption must be quickly diluted in a larger quantity of bouillon to prevent its bactericidal property. Neufeld advises cutting several fresh roseolar spots superficially, with the knife, without producing pressure, to scratch the subcutaneous tissue of the same, and the fluid gathered in this way should be at once diluted in bouillon. Neufeld's method has also shown itself of value in the hands of other examiners—Curschmann was successful fourteen times in 20 cases, P. Krause ³ had a positive result fourteen times in 16 cases. In the typhoid stools the Gaffky bacilli are usually found during the second week of the disease, from the tenth day of the affection onward. In the majority of cases they disappear from the stools about the fourth week in the course of the disease; in rare cases, however, they may be demonstrated in the feces even after defervescence. The demonstration of typhoid bacilli in the feces is so difficult (see below) that this method has not attained great diagnostic significance. The urine (and at the autopsy the kidney) not rarely contains the bacilli, especially in those cases in which complication with albuminuria exists. During the last few years a sudden excretion of large amounts of bacilli in the

¹ Berliner klin. Wochenschr., 1886.

² Zeitschr. f. Hyg. und Infectiouskrankh., Bd. xxx, p. 498.

³ Zeitschr. f. klin. Med., Bd. xli, p. 413.

urine has been recognized by various observers—Neufeld demonstrated this condition three times in 12 cases; Schicholdt, five times in 17 cases; Petruschky, three times in 50 cases—this appears suddenly from one day to the next, usually not before the end of the second week, frequently later, up to the period of convalescence, and occasionally in repeated attacks. This *bacteriuria* shows itself by marked opacity of the urine, occasionally occurring without any trace of albumin, and lasting for days, but it may also remain for several weeks. Regions that are more rarely the seat of the accumulation of bacilli may also be named: The expectoration from the lungs in some cases of typhoid pneumonia or broncho-pneumonia, the meninges in typhoid meningitis, the myocardium in typhoid myocarditis, etc.¹ It must be mentioned, finally, that typhoid bacilli have been repeatedly found in pus which appeared in connection with enteric fever or which developed secondarily; for example, in empyema in an encapsulated peritonitis, in cholecystitis, abscesses of the liver and spleen, purulent arthritic inflammations, thyreoiditis, orchitis, etc. It is noteworthy that the typhoid bacilli in these post-typhoid pus formations retain their property of life for an extraordinarily long time; they have been found alive after fifteen months, and even many years, after enteric fever has run its course.

INFECTION

Mixed and Secondary Infections.—The inflammation and pus-formation which occurs in the various organs, producing the complications and sequels of enteric fever, which are so frequent, are rarely due to the typhoid bacillus alone—although its pyogenic action cannot be questioned—but these conditions are most frequently the result of a *mixed infection* or a *secondary infection* with other micro-organisms. The bacterium coli, to which we shall refer explicitly later on, plays the chief rôle in this process; this organism is found as the generator of peritonitis, angiocholitis, etc. The streptococcus pyogenes is next in frequency; it is often demonstrated in secondary bronchopneumonia, otitis, etc. Streptococci are also found in the mixed infections of the severe septic forms of typhoid (streptococcus—typhoid—septicemia); it has been demonstrated experimentally (Vincent) that the presence of the streptococcus in artificial mixed cultures markedly increases the virulence of the typhoid bacilli. The staphylococcus, Fränkel's diplococcus, and the bacillus proteus frequently find opportunity to colonize in the organism which has become weakened by typhoid fever and give rise to furunculosis, cutaneous abscesses, gangrene, bronchopneumonia, etc.

Port of Entrance of the Infection and its Sources.—From numerous investigations, regarding the methods of distribution of the typhoid bacillus outside of the body and the mode by which it finds its way into the human organism, two propositions have resulted which may be looked upon as absolute facts:

1. *The Principal, most Probable Port of Entrance is the Digestive Tract.*—The typhoid bacilli are swallowed and enter the intestine, from which point they infect the body.

¹ The sputum of the bronchitis, which is so frequent in enteric fever, is free from typhoid bacilli (*P. Edel*, Fortschr. d. Med., 1901, No. 14); the same is true also of the sputum of pneumonia in enteric fever, but it frequently contains other bacteria, pneumo- and other cocci (*A. Fränkel*, Deutsch. med. Woch., 1899, Nos. 15, 16). That the expired air of enteric fever patients contains bacilli, as was noted by Sicard as a regular occurrence, can only be looked upon as an exception if it occurs at all; I was never able to find them.

2. *The Principal Source of all Typhoid Infection is Formed by the Bacilli-containing Stools of the Typhoid Fever Patient.*—By this means the bacilli reach the hands, the clothing, and other substances, find their way into the food and drink, into the earth, into the springs, into the water-supply, etc., which, directly or indirectly, further distribute the infection (besides the stool as a rarer source of infection, also the urine, in some few cases the sputum, and typhoid bacilli-containing pus).

Typhoid infection arises per os. We have previously called attention to the fact that the typhoid bacillus is not sensitive to acid; the hydrochloric acid of the gastric juice does not positively destroy it, so that even in a completely normal function of the previously mentioned barrier, the stomach, no certain protection against typhoid infection is given. The bacilli which have been swallowed reach the bowel and increase to a great extent in its feebly alkaline contents; they colonize in the follicles and plaques of the intestinal wall and here slowly originate the process which is the foundation of enteric fever, the medullary swelling, leading to necrosis and, by the desquamation of the necrosed areas giving rise to ulceration. The bacilli increase in the intestinal wall and reach the mesenteric glands, probably by way of the lymph channels, finding their way into the spleen, the liver, etc. The toxins, which originate in and from them, reach the circulation; their action upon the nervous system, heart, etc., gives the bowel affection the especial characteristics of the typhoid infection.

An infection by way of the lungs, which formerly played such a great rôle, is not very probable. The dry germs may find their way with the dust, the dirt of the streets, and from the clothing into the respiratory tract with the inspired air. Infection is therefore possible in this manner, and the view is even accepted by some authors, but this method of infection has not been proven.

True typhoid bacillus pneumonia is rare in itself, and in none of the few cases of so-called *pneumotypoid*, in which pneumonia occurs as a substantive affection, and so early that it appears clinically as the first localization of the causative factor of the disease, has it been determined that the case in question is not one of an unusually early complication by metastasis, so that the primary focus in the intestine is less obvious, and has originally been overlooked. We may, therefore, say: The occurrence of infection by way of the lung is questionable; if it occurs at all it is exceedingly less common compared with the extraordinarily frequent infection by way of the mouth. (Compare page 10.)

Infection by Contact.—Enteric fever does not belong to the actually contagious diseases; the mere presence of an individual in the vicinity of a typhoid patient is not dangerous. Contagion from case to case was formerly entirely denied. And yet it occurs and is even not so rare. Eschricht¹ reports—only to mention one of the many examples—a series of 5 cases in which, in an uninterrupted chain, the person that had previously nursed the patient was regularly attacked by enteric fever. Naturally, in this case we are not dealing with contagion in the old sense, but (as emphasized by the author himself, who excludes a drinking water infection in all 5 cases) with a reception of the product of infection by contamination from the patient, or from some of the material handled by him. And this is the usual mode of infection, which may be accurately followed in many cases. In nursing and caring for the patient,

¹ Zeitschr. f. Medicinalbeamte, 1900, No. 13.

in emptying the stools, in transporting or washing the clothing, typhoid bacilli from the dejecta of the sick reach the hands of the persons and, if there be insufficient cleanliness, may reach the food material and thus find access to the digestive tract. With these soiled substances, for example, commonly with the unclean underwear of the patient, which are given out to be washed, the germs find their way from house to house and may reach great distances—by transporting the washing, by post, or by express, even distant regions may be invaded—apparently independently and yet in direct consequence of a case to case infection.

Water Infection.—Of more frequent occurrence is the *indirect distribution*, which explains the outbreak of an increased number of cases, giving rise to the *appearance of epidemics*. The typhoid germs reach media in which they are uniformly distributed, eventually also multiplying, and spread to numerous districts simultaneously, which may not at all be in connection with one another, and this then gives an opportunity to numbers of individuals to take up the germs into their digestive tracts. Here also the evacuations of enteric fever patients form the point or origin. The chief rôle in this mode of distribution is played by WATER, the MAIN DISTRIBUTOR OF THE TYPHOID POISON. Even before the discovery of the typhoid bacillus the conspicuous connection between epidemics and contamination of drinking water and the distribution of the same had been recognized clearly in many cases. I shall relate a few especially instructive cases.

Liebermeister¹ reports an epidemic in Lausen (Canton Baselland) in 1872: "The village Lausen had not had an epidemic of enteric fever since 1814, when the allied armies marched through that region; some individual cases which were brought in from Basel never gave rise to a dissemination of the disease; in the last seven years there had not been a single case of typhoid fever. On the 7th of August, 10 inhabitants were attacked by enteric fever, and in the following nine days, 57 persons were affected. The epidemic lasted until October, and in the village, which scarcely contained 800 inhabitants, 130 were attacked, nearly 17 per cent.; of this number, 100 cases occurred in the first three weeks of the epidemic; besides these, 7 persons were affected that only transiently remained in the village, and the most of these, a short time after leaving the district. The disease only occurred in such houses as received their water supply from flowing wells. The houses which only used pump-water remained free from the affection. It was determined with certainty, that the water which supplied the running wells had a subterranean source, from a brook, in which some distance above the village, the privy and the dung heap of a certain house drained. In this house, on the 10th of June, a man had suffered from an attack of enteric fever, and in July and August, three further cases of enteric fever occurred in the same house."

Curschmann² relates the following example of a well infection: "Early in the seventies of the last century I treated, in a suburb of Berlin, which contained nearly 1,000 persons who lived in small, poorly ventilated rooms, a number of enteric fever patients. My investigation showed that at the same time about 80 patients were treated in the same house, some having been sent to the hospitals. Closer investigation showed that the water-supply upon this piece of ground came from one well (the general water-supply had not yet reached this region) and was seriously contaminated by organic substances; it was turbid and had a foul odor. A year previously, a similar condition of the water had been noted, the cause for it having been a communication with a large privy vault. The suspicion to which I gave expression, that now also such a contamina-

¹ Ziemssen's Handbuch d. spec. Pathologie u. Therapie, ii, 2te. Aufl., 1876, p. 64.

² Curschmann, Der Unterleibstypus, Wien, 1898. (Nothnagel's Spec. Pathologie und Therapie, iii, 1, p. 26.)

tion of the water with the fecal contents existed, and that this was the cause of enteric fever, was belittled by persons of authority, who said that at the previous time, with a similar contamination of water, certainly no case of typhoid fever had occurred in the district in question. My further investigation showed that this was quite correct, but another circumstance was developed that explained the apparent difference and caused my suspicions to become actual facts: Four weeks previous to the appearance of the first cases of enteric fever among the inhabitants of the suburb, 'a boarder' arrived, in whom gradually the symptoms of enteric fever appeared, and who was the cause of the disease appearing in two children in the family of the person with whom he lived. Now there can no longer be a doubt, as in the spring of the same year, that the water of the well was contaminated by fecal substances, and at that by an actual admixture of the specific germs of the disease which were the *conditio sine qua non* for the development of the disease."

These two instances, in which the distribution of the disease concerned comparatively small districts, may be complemented by "an illustration of the development and epidemic distribution of enteric fever upon a large scale, along the course of a great river" which was given by the conditions of Hamburg, during the eighties of the last century. This illustration is taken from Curschmann's¹ text-book.

In the years 1885 to 1888, 15,804 persons were attacked by enteric fever in Hamburg, with 1,214 fatal cases. Hamburg at that time obtained all of its drinking water and that used for other purposes from the Elbe; it was conducted into the houses without being filtered and was used for all purposes of the household and also for commercial purposes without being disinfected. Only the drinking water and the water used in the kitchen was filtered, but then with apparatus which, as we know to-day, on account of its faulty construction, rather damaged the water still more, instead of serving a useful purpose. Even during this time Curschmann called attention to the fact, that the production of the epidemic was evidently due to a specifically infected water. The contents of the Hamburg canals are emptied into the Elbe, and Curschmann assumed that this might be the cause of the infection of the drinking water, as the mouths of the sewers were not situated at a sufficient distance from the points at which the different water conduits were situated: during the period of flood a regurgitating wave would make it possible to empty substances from the sewers into the water-supply. That the water-supply and nothing else was the carrier and distributor of the typhoid poison, Curschmann deduced first from the simultaneous distribution of enteric fever over the entire city—a building-complex, situated in a portion of the city in which the disease showed very severe and stubborn conditions, remained free; that is, an armory which was not connected with the general water-supply of the city but obtained its water from wells situated on the premises—and secondly, that the neighboring city, Wandsbeck, the inhabitants of which town living under similar conditions, having the same climatic and temperature periods during this time, showed but very few cases. The condition which distinguished the two cities, which was emphasized by Curschmann, was the water-supply: Wandsbeck does not obtain its water from the Hamburg water-supply and not all from the Elbe.

Curschmann's views at that time were not credited. The great cholera epidemic again called attention to these conditions. Curschmann's assumption of a contamination of the water-supply from the mouths of the canals, was demonstrated by exact investigation (Reinke, Dunbar), and in 1893 the points from which the water was taken were moved much further up stream, and the water, before it reached the city, was subjected to proper filtration. The number of cases of enteric fever in 1892 was 1,941; in 1893 it was still 1,094, but in 1894 it was only 462, and in 1895, 597!

Similar Conditions.—Contamination of the water-supply from leakage near cesspools, into which enteric fever stools were emptied, infection of

¹ *Loc. cit.*, p. 27.

the river-water, so that the water-supply may be contaminated by canals or from ships on which there are enteric fever patients, etc.—have been met with so frequently in the last decade in typhoid epidemics, that there can no longer be doubt to-day of the markedly predominating etiological importance of the water-supply as the chief carrier and distributor of typhoid bacilli.¹ In Germany, especially R. Koch and his co-laborers, who have investigated numerous epidemics for the government, and lately the epidemic occurring in Gelsenkirchen, deserve great praise for having cleared up these conditions. Upon several occasions, and in spite of the great difficulty of their identification (see below), the typhoid bacilli have been found in water. In other countries, the connection between water and enteric fever has also been determined and generally recognized. The typhoid epidemic in Paris,² which will be the last example that I will quote, belongs to the best studied instances and it is one that has been thoroughly investigated.

A typhoid epidemic was present in Paris in the year 1899, which reached its acme in the autumn. As the origin of this epidemic the water of the Vanne was recognized, which supplies the low-lying portions of Paris. The higher situated points of the city which received water from the Avre and the Dhuys remained free from the disease. On the other hand, in the small town of Sens, which is also supplied with water from the Vanne, there was a decided epidemic of typhoid. In the water of the Vanne as well as in the Paris water-supply at different points, Eberth-Gaffky bacilli were demonstrated. The following was determined regarding their origin: 12 kilometers from the source of the Vanne, upon a high ground with a chalky deposit, there is situated a village in which, prior to the outbreak of the epidemic of typhoid fever in Paris and Sens, typhoid fever existed. Below the village, in the earth which is filled with fissures and spaces, the source of the Vanne is found (Arago, Hanriot).

Food Infections.—Besides the water, certain FOODS play a part which, under special conditions, may transmit the disease to far-lying districts. First among these is milk, which not infrequently has been the cause of smaller or larger epidemics. In a collection by Schleghtendal³ 24 of such epidemics are noted which could be traced with certainty to the milk supply. One of these epidemics showed 289 cases of enteric fever. The investigation of such instances showed, with but very slight variation, the same conditions: In the neighborhood of a dairy there was a case of enteric fever, and the milk was mixed with infected water or infected by contaminated hands or vessels; since the milk is a splendid culture media for the typhoid bacilli, as we have previously stated, and is not altered in appearance by the presence of these bacteria, the germs of the affection may easily gain access to the houses of the consumers.

As the milk, so also *butter*, in which typhoid bacilli may remain living for a long time, may be the carrier and the distributor of the typhoid poison. Carbonated waters and others, which are manufactured with infected water, must also be considered; as the resistance of the typhoid bacillus to cold is

¹ *Schüder* (Zeitschr. f. Hyg. u. Infectiouskrankh., Bd. xxxviii, 1901) collected from literature from 1870 to 1889 a total of 638 epidemics of enteric fever, of which 77.4 per cent. directly (70.8 per cent.) or indirectly were proven to be due to infected water.

² *Annal. d'hygiène publ. et de méd. légale*, Mars, 1900, and *Centralb. f. Bakteriologie*, etc., 1901, p. 911.

³ *Deutsche Vierteljahrsschr. f. öffentl. Gesundheitspflege*, 1900, Heft ii.

well known *ice* may also become dangerous. Alcoholic drinks are less dangerous as alcohol shows a certain disinfecting power towards the typhoid bacillus. *Vegetables* and *fruit* which are cleansed with infected water should also be mentioned and, finally, a food substance which on several occasions has been the source of enteric fever, *oysters*. Fattening them in contaminated water must be looked upon as the source of the infection, and thus we find, in all these infections by food substances, the actual point of origin of the disease proves to be almost constantly the water.

Infections Through Air and Ground.—In comparison with the enormous importance of water for the distribution of enteric fever, the two other factors which formerly played a part in the supposed causation of the disease, *ground* and *air*, are almost insignificant. Especially air as the carrier of the virus, is scarcely of importance; all the former experiences regarding the transmission of the infection by the air will not stand criticism.

Liebermeister ¹ in 1876 still quotes a case of Gietl as an example of infection by the AIR as "very instructive": The evacuations of a typhoid patient were thrown upon a dung heap; among 5 persons who a few weeks later were occupied in carting this dung heap away, 4 were taken ill of enteric fever and 1 with gastric symptoms, with enlargement of the spleen. Unquestionably the assumption of the typical infection per os, transmitted by contamination of the hands, the clothes or food material of the workmen, would be much nearer the truth than that which Liebermeister assumed at the time as "completely justified," believing that the typhoid fever arose "by the inhalation of the exhalations of the typhoid stools."

Naturally, the further distribution of the dried germs by the air is not to be denied; this is certainly possible, and the inhalation of the bacilli with dust occurs, though very rarely, in fact. But these air infections are by no means pulmonary infections, the usual course being that the inspired bacilli remain in the upper parts of the respiratory tract until they are swallowed and taken into the digestive tract with saliva or food particles.

The ground may contain the typhoid germs in a living condition for a long time, as has been previously remarked. Repeatedly in excavations of the earth, in carrying out large enterprises which require turning the earth, enteric fever has been seen to originate in the workmen thus engaged and to distribute itself rapidly. This is readily explained by a previous contamination of the earth with typhoid stools and stirring up the quiescent germs by turning the earth. This may naturally give rise to the occasional inhalation of germs, but it is certainly much more common that the germs are taken into the susceptible organism by unclean hands, contaminated food, etc.

[The common house-fly plays an important rôle in the dissemination of the germs of enteric fever. This mode of conveyance from the improperly constructed latrines to the improperly protected food of the soldiers was common in the Spanish-American and in the South-African wars. Without doubt, many of the instances of supposed aerial transmission are to be explained in this way. Vaughn's studies of the subject are most convincing.—Ed.]

The *ground-water* may be active in the distribution of the infection, in that it floods out the germs which have remained upon the bottom, thus reaching wells or the source

¹ *Loc. cit.*, p. 60.

of the water-supply. But no support for the old Pettenkofer theory is gained by this. A connection between the ground-water and the frequency of enteric fever has only been proven for Munich; in many other cities this condition does not prevail at all. And, above all, the hypothesis of Pettenkofer, that the germs undergo a change in the earth, a purification process, has proven to be incorrect.

Thus the important fact remains that the distribution of the typhoid bacillus with the water, in connection with the direct transference from case to case, is able to explain all arising infections. The principal point of origin of every epidemic and of every case is always an individual affected by enteric fever.

BACTERIA AS CAUSES OF ENTERIC FEVER

We must now discuss the question: What proofs have we that this bacillus, the distribution of which we have just studied, is actually the cause of enteric fever? We have seen that it occurs in every case of typhoid fever. Its distribution in the body of the sick and its biologic conditions are in direct uniformity with the clinical phenomena of the disease. These are very important facts, but they are not sufficient. One condition is absent, and that the most important, to characterize a parasite as the exciting cause of an infection: We are not able to produce enteric fever experimentally with the typhoid bacillus. We have already called attention to the fact that in nature the animal world is not susceptible to enteric fever. This explains the negative results in animal experiments, but the link in the chain of proof remains; an important factor is absent. To this another important fact is added: The great similarity of the typhoid bacillus to the bacterium coli, the normal inhabitant of the intestinal canal and, further, the similarity of the bacillus of enteric fever with certain water bacteria. This similarity exists to such an extent that some authors (G. Roux in Lyon) maintain the identity of the typhoid bacillus and the bacterium coli, and this increases the difficulty of answering the question whether the typhoid bacillus only occurs in enteric fever or whether it is also found in other diseases? How much depends upon the etiological importance of the Eberth-Gaffky bacillus in the decision of this question requires no explanation; it is obvious that the typhoid bacillus stands or falls with the decision of this question. This is the reason that in the entire realm of the bacteriology of enteric fever, more attention has been devoted to this point than to any other. Numerous investigators have busied themselves with the differentiation of the typhoid bacillus from the bacterium coli, and it may now be maintained without any doubt that the typhoid bacillus and the bacterium coli are not identical. Naturally, the differential points between both are so slight and so inconstant that even to-day it belongs to the most difficult of bacteriological investigations to identify the typhoid bacillus in the individual case, i. e., to differentiate it from the very numerous typhoid-like intestinal and water bacteria with certainty. In the following chapter we must naturally enter into these differential points explicitly; *the specificity of the typhoid bacillus and its etiologic importance* depend upon this as we have previously stated.

Differentiation of the Typhoid Bacillus from the Bacterium Coli.—The microscopical behavior, the cultures upon gelatin and agar for both bacteria

are absolutely similar. The potato culture is usually—but by no means always—different: The bacterium coli shows a thick, raised, demarcated, smeary, brownish growth; the typhoid bacillus, on the other hand, an invisible, distributed coating. In using the potato for differentio-diagnostic purposes, one and the same potato divided in half, must be inoculated; one-half with the suspected bacillus, and the other half with a positive typhoid bacillus (see below). If upon both halves a like growth occurs, upon further similarities the probability is almost certainty that we are dealing with the specific Eberth-Gaffky bacillus. As important differentio-diagnostic points between the typhoid bacillus and the coli bacillus, the following points are important: 1. The bacterium coli coagulates milk, the typhoid bacillus does not; 2. The bacterium coli in the incubation oven even after the brief space of a few hours, forms a peptone-containing gas (this is especially marked if the culture media contains grape sugar); the typhoid bacillus does not; 3. The typhoid bacillus forms less acid than the bacterium coli (this bacillus reddens litmus much more markedly than the typhoid bacillus); 4. The bacterium coli gives an indol reaction (a red color upon the addition of 1 cc. of a 0.02 per cent. nitrite of potassium solution and of a few drops of sulphuric acid to 10 cc. of bouillon), the typhoid bacillus does not. The presence of these tests increases the probability obtained by the potato that we are dealing with a bacillus identical with the typhoid bacillus; this almost becomes a certainty. However, it must not be concealed that, although very rarely, there are varieties of coli bacilli which do not coagulate milk, do not ferment with grape sugar and that do not produce indol, therefore cannot be differentiated by these methods with certainty from the Eberth-Gaffky bacillus.

Quite a number of culture media have been advised which show a variation in growth between the typhoid bacillus and the coli bacillus. I shall mention the Elsner method, which is advised to employ in cultivating typhoid bacilli from the feces: Plates are covered with potato gelatin to which is added, shortly before use, iodide of potassium in the proportion of 1 per cent. After forty-eight hours the typhoid colonies are visible as small, water-clear drops, whereas the much more energetically developed coli colonies are noted as large, dark brown, globular masses. The Elsner method shows a great advance, but even this is not absolutely positive; it requires great practice and does not obviate the exact identification of the colonies recognized as typhoid bacilli by all the other known methods, as some typhoid-like bacteria (especially the *Bac. fæc. alcal.*) show very similar conditions, under some circumstances resembling the typhoid bacilli.

As of still more value for a culture media, for differentio-diagnostic purposes, many authorities praise Piorkowski's urine gelatin (urine which has spontaneously become alkaline is decomposed with a $\frac{1}{2}$ per cent. peptone, 3.3 per cent. gelatin; cooked over a water bath for one hour, immediately filtered, sterilized at once for fifteen minutes, and upon the following day again for ten minutes). Upon this culture media typhoid bacilli, after from fifteen to twenty-four hours, form irregularly constituted longitudinal colonies which are surrounded by a fine marginated network of processes, which principally extend from the poles of the longitudinal colonies. The coli bacteria, on the other hand, grow in larger, oval colonies. It must, however, be remarked here that, as valuable as the Piorkowski method is, it does not give absolute certainty, as some motile coli varieties form sparse stumpy processes, some few, although this is rare, even show the characteristic fine and round processes, which are noted in the typhoid bacillus.

Lately Drigalski¹ has suggested a colored culture media in which, by the addition of crystal violet to litmus agar, the typhoid bacilli grow with a blue color with a tinge of violet, the coli bacilli showing a bright red color in growth (the coli colonies after

¹ Zeitschrift f. Hyg. u. Infectiouskr., Bd. xxxix, Heft ii.

twenty-four hours are larger and opaque, the typhoid colonies are smaller, dew-drop like). The difference in color, which I have determined by a test with pure cultures, is very demonstrative; whether the method will meet the requirements of practical tests remains to be seen.

In spite of all these aids, the differentiation between typhoid and coli bacilli has remained an exceedingly difficult one, and only such bacteria could be determined with complete certainty as typhoid bacilli, which showed all the properties of typhoid bacilli and which were taken from the spleen of human beings (by puncture or at the autopsy immediately after death), who had shown all the clinical phenomena of enteric fever.

Newer and more reliable methods, for the differential diagnosis between the Gaffky-Eberth bacillus and the great number of typhoid-like intestinal and water bacteria, have been gained by the Pfeiffer and Gruber-Widal reactions. R. Pfeiffer recognized that a guinea-pig immunized against typhoid bacilli developed the property of dissolving typhoid bacilli in an intra-peritoneal inoculation. The bacteria become immotile immediately after the injection, they swell, and after a few minutes show a beginning decomposition into small globules, until after about fifteen minutes only fine granules are found as the residue of the dissolved bacteria. In tests which are taken from the abdominal cavity of the animal from time to time by means of fine glass capillary tubes, the process of dissolution may be followed step by step. This *lysigenous* (dissolving) property is a strictly specific one, only that variety of bacteria will be dissolved in the peritoneal cavity against which the animal has become immune. The guinea-pig, immunized against typhoid bacilli, only dissolves typhoid bacilli, not coli bacteria; the animal immunized against coli bacilli, only dissolves coli varieties, not typhoid bacilli. With this fundamental Pfeiffer discovery, a certain differential method for the separation of typhoid bacilli from all other bacteria resembling it, and the specificity of the typhoid bacilli was demonstrated for the first time. Pfeiffer then modified his method in the manner, that the bacilli were not injected into an immunized animal but into one that was not previously so treated, but mixed with a minimal amount of serum which was taken from an immunized animal; the addition of the immunized serum acts in the same specific manner, gradually dissolving the injected bacteria. Pfeiffer also recognized that in this manner the quantitative proportions were of great importance: The normal serum of animals that are not immunized may give the reaction, i. e., show a *lysigenous* property, but only upon the addition of relatively large amounts; whereas of the immunized serum, minimal quantities are sufficient. Pfeiffer's reaction is now practiced in the following manner: Ten times the minimal lethal dose is added to the bacteria variety that is to be tested with an amount of serum slightly below 0.1 cc., which is taken from an animal markedly immunized against enteric fever, the entire amount being injected into the peritoneum of a guinea-pig. In from ten to twenty minutes in the exudate, which is taken by means of glass capillary tubes from the abdominal cavity, the previously described dissolution of the bacteria into granules is shown, we are dealing with true typhoid bacilli.

A second reaction, much more simple and, therefore, generally practiced, and which is of marked differentio-diagnostic importance, depends upon the

phenomenon of AGGLUTINATION, Gruber having given it this name. The serum of animals that have been immunized against enteric fever, and also of human beings that have recovered from typhoid (and in this way have acquired immunity), act in a small quantity of a typhoid bouillon culture in a peculiar manner: The bacteria become immotile, collect in clumps and fall to the bottom of the test tube as a flocculent precipitate, whereas the fluid above remains clear. This reaction of the immune serum, which was previously described by various authors, especially Bordet, without, however, having appreciated it correctly, was minutely studied by Gruber and Durham, somewhat later by R. Pfeiffer and his pupils. The agglutination test is usually employed in the manner that to a twenty-four-hour old bouillon culture a certain quantity (see below) of typhoid immune serum is added and this placed in an incubation oven at 37° C.; the beginning of the reaction is designated by the formation of the smallest granules and flakes in the previously uniformly turbid bouillon, and in the continuance of the process, the bouillon clears more and more, the flakes become more dense and fall to the bottom until finally the clear bouillon is found above the flocculent precipitate. Agglutination may also be well followed under the microscope: In a hanging drop, the previously-acting motile bacilli, separated from one another, collect in heaps or islands in which they become absolutely immotile.

In the Gruber reaction the quantitative proportions are also to be accurately noted, as the serum of normal animals and human beings shows agglutinating properties. But normal serum at most agglutinizes in the proportion of 1 to 10 (i. e., upon the addition of 1 drop of serum to 10 drops of bouillon), usually in proportion of only 1 to 5 or even less dilution; only exceptionally in human beings has a proportion of 1 to 30 or even 1 to 40 been determined. The agglutinating power of normal serum of rabbits, horses, and donkeys varies between 1 to 30 and 1 to 50; the serum of guinea-pigs that have not been previously treated, as a rule, does not agglutinate at all. The serum of immunized animals, on the other hand, shows agglutination even in dilutions of 1 to 50, 1 to 75, 1 to 100, and even much beyond this, reaching into many thousands. We may, therefore, say: If a bacterium resembling the typhoid bacillus does not show agglutination with the serum of an animal that has been highly immunized against the typhoid bacillus in the proportion of 1 to 10, it can not be the typhoid bacillus. If the reaction results positively, this is markedly in favor of it being the typhoid bacillus: the identity only becomes certain, however, if agglutination occurs also with the addition of the immune serum in the proportion of 1 to 50, 1 to 75, and 1 to 100. It is not necessary to determine the limit of the agglutinating power, which may be best accomplished microscopically; the determination of agglutination at 1 to 100 is sufficient to establish the diagnosis.

With this method, a relatively simple, easy and reliable process is given for the differentiation of the bacterium coli and other typhoid-like bacilli from the typhoid bacilli.

Serum Diagnosis of Enteric Fever.—The Gruber reaction has been still further developed, which is of great importance for clinical diagnosis. Whereas Gruber looked upon agglutination as an immunity reaction, Widal showed that in man at least it was a reaction of the period of infection. He demonstrated that the blood serum of enteric

fever patients, at the end of the first or at the beginning of the second week of the disease, shows in a pronounced manner the agglutination phenomenon with typhoid bacilli even in great dilution. The serum of healthy persons or those affected by other diseases—according to Widal and Sicard—does not agglutinate at all or only in proportions of 1 to 10, rarely 1 to 20, and only in exceptional cases a greater dilution, 1 to 50. The serum of typhoid patients agglutinates in dilution of 1 to 50, 1 to 100, up to 1 to 1,000, 1 to 3,000, and even up to 1 to 5,000. In one case Widal showed an agglutination in a proportion of 1 to 20,000. Widal and Sicard advise looking upon reactions varying between 1 to 10 and 1 to 50 as suspicious of enteric fever, and to repeat the test in the next few days. The proportion of 1 to 50, however, in their opinion, is sufficient to decide a positive diagnosis of enteric fever. The property of agglutination appears, after Widal's investigations, to occur in the serum of typhoid patients about the seventh day, in some cases later, in a few even sooner.

The time of the appearance of the Gruber-Widal reaction, its intensity and duration, above all, its occurrence in affections that are not typhoid, has since then been investigated by numerous authors in thousands of cases. It is impossible to name here any but the most important of the many points determined in this field. The results may be mentioned in the following: The reaction is peculiar to enteric fever, it does not occur in healthy individuals, nor in other diseases. However, the quantitative proportion is alone determining—only in dilutions of over 1 to 50 is the positive result a proof of typhoid; values of 1 to 10 and 1 to 20 prove nothing—and also the rapidity of the appearance of the reaction deserves recognition. The rapid appearance of the reaction is especially diagnostic: If the bacteria after the addition of serum (under the microscope) become immotile at once, if they clump together immediately in a heap, a greater dilution, above 1 to 75 or 1 to 100, is unnecessary. The positive result of the agglutination test applied in this manner is absolutely diagnostic. The agglutinating property of the serum does not occur so frequently as Widal assumed, only in a small number of cases can it be noted towards the end of the first week of the disease, usually only in the second week of the disease, between the seventh and the tenth day, does the reaction appear. The negative reaction in the first week, therefore, is not against the diagnosis of enteric fever. Conclusive—even though of great importance—is not even the negative result during a later period, as in rare cases the agglutinating property of the serum only shows itself during the third or fourth week or even during the period of convalescence. Such cases have been noted repeatedly; Curschmann¹ observed it twice, and also Liebermeister reports a case (compare page 20); a case of Schumacher,² which terminated fatally, neither intra-vitam nor post mortem, showed the Gruber-Widal reaction. These cases are rare; they belong, according to Curschmann, to the "greatest exceptions," but the literature contains quite a number of them. In judging the positive results of the reaction another factor is to be considered, its duration after enteric fever has run its course. Widenmann³ examined 67 cases, from a quarter of a year to forty-five years after an attack of enteric fever, in 49 cases agglutination was absent, and Widenmann propounds the law, that the Gruber-Widal reaction disappears one year after enteric fever has run its course; in the cases in which it is still present, it is absent in the dilution of 1 to 100 or only occurs after several hours, and then not very completely. But exceptions to this rule are not few; Widenmann determined the reaction in his cases once after seven, ten, eighteen, twenty-one, and even after twenty-seven and thirty years. A positive reaction, therefore, in a suspected febrile case, may be due to a previous typhoid, and not due to the disease in question. Usually the history will protect us here; but we dare not undervalue this source of error, all the more, as it has been determined that even a very mild attack of enteric fever which may not even have been recognized as such, but designated as a "status gastricus," may be combined with a decided and long-continuing agglutination.

Regarding the property of the agglutinating substances and the nature of agglutination, we are as yet not clear. Gruber's view, that the power of agglutination occurs with immunity, has been shown to be untenable. The property of agglutination has been

¹ *Loc. cit.*, p. 406.

² *Zeitschr. f. Hygiene*, Bd. xxx, p. 364.

³ *Charité-Annalen*, xxv u. *Deutsche Militärärztl. Zeitschr.*, 1901, No. 1 und 2.

shown to occur very early, once upon the second day of the disease, therefore at a period when there could be no question of immunity. It has been determined that relapses are just as frequent with a marked as with a weak property of agglutination (Tobiesen¹ and others). But also against Widal's opinion, that agglutination is an expression of the infection, many exceptions may be taken. The severity of the infection is not parallel to the power of the agglutination reaction, in the agglutination curve of one and the same individual, inside of twenty-four hours, marked variations occur (Pamart); above all, severe lethal cases, as has been mentioned above, may occur without giving the reaction. All these conditions influence the diagnostic importance of the Gruber-Widal reaction, the negative result of which in the individual case must be judged with caution. With a positive result, however, in the above-mentioned sense, it unquestionably has great diagnostic value and signifies a universal, generally recognized enrichment of our diagnostic methods.²

The significance of the Pfeiffer and the Widal-Gruber reaction is—apart from the previously described practico-diagnostic value—an extraordinary one. These methods alone have made it absolutely certain that the typhoid bacillus is different from all other similar micro-organisms, that it is a specific bacterium, and that enteric fever is in a characteristic specific relation to it. The question propounded above, whether it is proven that the typhoid bacillus is the exciting cause of enteric fever, we may positively answer in the affirmative.

PREDISPOSING CAUSES

It still remains to discuss those etiological factors besides the bacillus, which play a part in typhoid fever. It is true of enteric fever, as of other infectious diseases, that the taking up of the germs is not synonymous with infection; especial predisposing factors which favor the development of the disease must be added.

A predisposition as regards locality can no longer be assumed for enteric fever. The disease occurs all over the world with about a like frequency. If some districts are relatively free or even without enteric fever, others showing greater typhoid morbidity, it is still unjustifiable to speak of typhoid immunity and typhoid districts; the denseness of the population and the conditions of inter-communication of the districts in question, their better or poorer hygienic conditions, explain the variation in the prevalence of the affection in a sufficient manner, without there being a necessity to attach any special importance, in the sense of the local theory of Pettenkofer, regarding the condition of the ground and the ground-water.

A certain predisposition, however, in regard to time, the influence of the season of the year upon the frequency of enteric fever, cannot be denied. The

¹ Zeitschr. f. klin. Med., 1901, Bd. xliii, Heft i.

² The agglutination test is also of use to the practitioner who is not in possession of a laboratory, as the blood, if taken sterile and saved (at best in an inoculation tube, which may then be closed), may be sent to some distance for examination. It is then necessary to determine the amount of the fresh blood; after dissolving the dried blood in a measured quantity of a physiological salt solution the agglutination test may be tried in the usual manner. The blood is taken with a syringe from a vein of the arm or by a wet cup. In private practice, especially if the investigation is to be carried on in the immediate vicinity, it is sufficient to take about 20 drops of blood from the lobe of the ear or the tip of the finger.

malady is much more frequent in autumn than in spring; the months from August to October in general are those which show the greatest number of cases of the entire year; the months from March to May are the ones in which the least number of cases occurs. This has to do with climatic influences; which factors of the climate however, are peculiarly active has not been clearly determined. Many experiences are in favor of the dryness and heat of the summer showing an increased frequency of the affection in the following autumn. On the other hand, marked rains are frequently brought into relation with the distribution and epidemic prevalence of the disease. Principally, observations of this kind were the support of the ground-water theory. They may be partly explained even without this—prolonged rains and inundations (melting of snow) which carry faecal matter containing germs into the earth, conveying them into wells and into the water-supply—partly the conditions cannot be explained.

Regarding the influence of age, youth, the years from fifteen to thirty-five are especially predisposing. Above and below this age, the number of cases rapidly diminishes; in the first year of life enteric fever is very rare, the same is true after the fiftieth year of life; no age is entirely free. Both sexes are liable to the same extent; that enteric fever is more frequent in the male sex has been proven by statistics, as has also the formerly assumed view, that enteric fever is more severe in the female. Some occupations predispose to enteric fever—and this may perhaps explain the occurrence in greater frequency in one or the other sex, which may result in the preference for one or the other sex—there should be mentioned laundresses, laborers, canal-workers, seamen, etc. The occupation of nurse I need fortunately not mention. In our hygienically instituted and well-conducted hospitals the nurses are not attacked by enteric fever any more often than the other occupants of the wards; no mention is made to-day of the formerly so notorious nosocomial typhoid. Of an especial constitutional predisposition, little has been noted. Well nourished, strong individuals are attacked as frequently, even with more frequency, than thin, poorly nourished individuals. Over-exertion of a bodily or a mental nature, overwork, anxiety, sorrow, appear to increase the susceptibility to enteric fever. A connection between refrigeration and similar conditions has not been proven nor is this possible; enteric fever has no special connection with any other infectious disease. In well-developed tuberculosis, enteric fever occurs only exceptionally—cachectic individuals are but very slightly predisposed to enteric fever; tuberculosis, however, does not by any means exclude enteric fever—in an incipient tuberculosis, enteric fever is not so rare; phthisis, which has been latent up to that time, becomes manifest by an attack of enteric fever and runs a rapid course.

The puerperium and the period of lactation, as well as pregnancy, are said to convey a certain protection against typhoid. This cannot be proven as regards pregnancy. Pregnant women, although not attacked more frequently, are by no means more rarely affected by enteric fever than are other women. In the majority of these cases typhoid causes abortion, or premature birth. Infection of the fetus has been bacteriologically demonstrated in some few cases; it cannot be maintained that this is the rule.

The only protection against enteric fever, which has been determined

with certainty, is conveyed by recovery from the disease itself. Enteric fever must be counted among those infectious diseases that confer immunity. But this protection is not absolute, at least not for an unlimited time. Second attacks occur—Curschmann determined it thus 54 times (2.4 per cent.) in 1,888 cases—even a third attack, and more frequently than this even, though rarely, have been observed.

II. DIAGNOSIS AND PROGNOSIS OF ENTERIC FEVER

By C. LIEBERMEISTER, TüBINGEN

DIAGNOSIS

The conception and diagnosis of enteric fever have undergone great changes in the course of the last century. The expression typhus (τῦφος) originally signified smoke, vapor, then also a befogged condition of the senses. The expression was principally used in certain cases of disease in which the severe, depressed condition of the psychical functions was a conspicuous symptom. Although in the Hippocratic writings a number of different conditions were designated by the name typhus, this very descriptive name, which portrays the symptoms so accurately, was never in general use among the ancient physicians. As a designation for a special group of affections, the name typhus was introduced into pathology by Boissier de Sauvages,¹ and he described special varieties such as typhus carcerum, nervosus, comatosus, castrensis, icterodes (yellow fever), etc. With this also a typhus hysterico-verminosus and a typhus exhaustorum and, finally, even certain intoxications, as varieties of typhus. In a similar originally purely symptomatic sense, the name typhus gradually came into general use, in that primarily such cases of disease were included in which a well-developed status typhosus was noted, and not only then if a symptom-complex which we now designate as typhus, was present, but also if pneumonia, variola, scarlatina, pyemia, puerperal fever, uremia, etc., were the underlying conditions. By others the conception was somewhat more limited, and principally diseases were included which were previously designated as febris nervosa, maligna, continua, putrida ardens, pestilens, bellica, castrensis, petechialis, etc. The milder cases which are at present designated as typhus, in which the peculiar "typhoid" symptoms were not developed, were not counted as typhus, but were designated by another name, as, for example, febris simplex, gastrica, mucosa, biliosa, continua, non putrida, etc.

With the beginning of the domination of a pathologico-anatomical standpoint, it was attempted to erect an anatomical, uniform, morbid picture under the conception of typhus. Previously even to this, the intestinal affection had been described as an isolated finding, being more or less accurately described; there was noted from the beginning of the last century with increasing fre-

¹ *F. Boissier de Sauvages, Nosologia methodica, T. I. Amstelod., 1768.*

quency, and especially in France (A. Petit and Serres, Broussais, Bretonneau), in numerous cases a conspicuous and characteristic lesion in the ileum and mesenteric glands, and epidemics appeared, in which all cases upon which an autopsy was held, showed these pathological changes exclusively. Upon the basis of this, it was believed to be justifiable to regard this finding as characteristic of typhus and to assume that the disease was a local affection of the intestinal canal, a gastro-enteritis, enteritis follicularis, dothien enteritis, furunculosis of the mucous membrane of the intestine, as an enanthema in contrast to the acute exanthemata. Simultaneously, other cases were observed which could not be differentiated symptomatologically from the previously mentioned ones in which, however, the intestinal lesion was not present; this condition arose, especially in England, quite constantly, marked epidemics occurring, whereas under circumstances, typhus occurred simultaneously with and without intestinal ulceration. Only with great difficulty were the French and English physicians able to decide that their subjects of investigation were different. Gradually several varieties of typhus were set up, which were to be differentiated by the various local affections and which were designated as abdominal typhus, cerebral typhus, pneumo-typhus, laryngo-typhus, exanthematic typhus, etc. With this, some few physicians recognized these diverse varieties as actually different diseases, whereas the majority only looked upon the anatomical findings as a difference of localization of one and the same general affection.

These points of view were completely changed when the etiological principle of division was gradually accepted for the infectious diseases. To decide the question of the identity or non-identity of the typhus forms, it was no longer conclusive to find a similarity or difference in the symptoms or in the pathologico-anatomical findings; these connections were only of secondary importance. The etiology alone was decisive, and all other factors only, in so far as they offered evidence of agreement with or difference from the etiology. The question had now to be formulated as follows: Does the same causative factor give rise to all forms of typhus, which may constitute itself differently under varying circumstances, showing another localization? Or do the various forms depend upon the action of specifically different pathogenic agents? This question was decided, with complete certainty against the believers of the unity and in favor of those that assumed different causative factors. It was shown, and is to-day generally acknowledged, that among the affections which were grouped together as typhus, at least three specifically different diseases could be recognized, of which each one depended upon a special pathogenic agent. These diseases are typhus fever (exanthematic typhus), enteric fever (typhoid, abdominal typhus), and relapsing fever (febris recurrens). Repeatedly during the third decade of the last century, the non-identity of the various forms of typhus was maintained; it was particularly William Jenner¹ in England, and Griesinger² in Germany, who were the pioneers of

¹ W. Jenner, On the Identity or Non-identity of the Specific Cause of Typhoid, Typhus and Relapsing Fever. Med.-chirurg. Transact., vol. xxxiii, 150, p. 23.—Lectures on the Acute Specific Diseases. Med. Times and Gazette, 1853, March 5, *et seq.*

² Griesinger, Infektionskrankheiten. In Virchow's Handbuch d. spec. Path. u. Ther., Erlangen, 1857, p. 118 ff., 2te. Aufl., 1864, p. 145 ff.

this view and they are most responsible for having brought the specific difference of these affections into general notice. In France, the Crimean war, in which the French physicians had an opportunity for becoming more intimately acquainted with typhus fever (*typhus exanthematicus*), was decisive for its separation from typhoid fever (*abdominal typhus*).

An entirely new classification of diseases arose, in carrying out this etiological principle of division. The severe forms of *febris nervosa*, *maligna*, *putrida*, could no more be looked upon as identical, but were recognized as belonging to different affections. On the other hand, the mild forms of *continua simplex* or *febris gastrica*, which frequently showed no suspicion of typhoid phenomena, in so far, as they were produced by the same pathogenic agent, were looked upon as identical with the severest typhoid affections, and were placed with the varieties of typhoid. Finally, the discovery of the specific cause of enteric fever followed, which justified the recognition of the etiologic principle of division as correct.

As a result of this progress, the diagnosis of enteric fever is placed upon an entirely different footing. We are concerned no longer with recognizing a distinct symptom-complex and in designating it correctly, or in drawing conclusions from the symptoms, or the presence of certain pathologico-anatomical changes; it is our duty to determine whether, in the special instance, the morbid phenomena which are present are due to the specific pathogenic agent that gives rise to enteric fever.

This condition can most certainly be determined by the demonstration of typhoid bacilli in the body of the sick or in his dejecta. In fact, in doubtful cases, this demonstration is of conclusive importance. The bacilli may be found in the fecal evacuations of the sick, in the blood, especially that taken from the spleen, in the eruption, in the urine, and, in cases which run a fatal course, also in the specific pathological products of the intestine, the mesenteric glands and in other organs. But this proof is not very easy, and the differentiation from other bacilli, especially of certain forms of the *bacterium coli*, is difficult;¹ great practice is required in bacteriological methods and, for the most part, a longer observation of the cultures is necessary. For this reason, in ordinary practice this method of investigation will hardly become so general and so conclusive as the examination for tubercle bacilli in tuberculosis.

Of great importance in diagnosis is the agglutination test of Gruber and Widal,² which depends upon the property of the blood serum of typhoid patients, added to a fresh bouillon culture of bacilli to produce an agglutination of the bacilli, so that they collect in small masses and sink as a flocculent precipitate. It must be noted, that the reaction is only then decisive, if agglutination occurs upon the addition of a greatly diluted serum (1 to 50 or 1 to 100), that the reaction does not occur at the onset of enteric fever but only during the course of the second week of the disease, and that the serum of persons that have recovered from a previous attack of enteric fever may also cause agglutination, even if they are not suffering from typhoid fever at the time at which the test is made. In some few cases, even in unquestioned enteric fever, the reaction does not occur. It

¹ Compare p. 15.

² Compare p. 15.

occurred in the clinic at Tübingen, that the agglutination test was negative in the entire course of the affection of a patient who died during the third week of the disease, who showed the most pronounced phenomena of enteric fever, and at the post-mortem, the characteristic changes were found in the intestine and in the other organs. On the other hand, the blood of unquestioned enteric fever patients has been utilized to recognize questionable bacilli as typhoid bacilli by their property of agglutination. The agglutination test is frequently of decisive importance in cases in which the symptoms are but feebly developed, or in which the differential diagnosis, from other severe maladies, gives rise to difficulty. In general practice, the test will only be utilized to a limited extent, for the reason that the practitioner, as a rule, is not in possession of fresh cultures of typhoid bacilli.¹

The so-called diazo-reaction of the urine, which for a time was believed to be a diagnostic aid, has but slight importance, as it is occasionally absent in well-developed enteric fever and is present in many other febrile diseases.

For this reason, the diagnosis of enteric fever in general practice, even after the discovery of the typhoid bacillus, depends upon the same aids which were formerly in use, namely, the careful observation and examination of the patient. The value of individual morbid phenomena, signs, and symptoms have undergone changes, however, in various directions; this is especially the case and to a marked extent, regarding the symptom-complex, which has given it the name of "typhoid."

At present we still speak of a *status typhosus* if a patient shows marked involvement of the sensorium, if muttering delirium is present, accompanied with subsultus tendinum and carphologia, or a soporous condition without actual sleep is present, from which the patient can only be aroused by energetic measures, such as the production of pain, etc., only retaining consciousness transitorily; usually, to the symptoms of this condition are also added other phenomena, such as a dry and fissured condition of the tongue and lips, a fuliginous coating of the lips, tongue and gums. This is particularly the condition to which the older physicians gave the name of *febris nervosa stupida s. torpidá*. This condition arises in enteric fever, with high continued fever, particularly if this symptom is treated improperly or not at all. In hospital practice we see it occasionally in patients who only come under treatment at a far advanced stage of the affection; but it is also noted in severe cases of the acute exanthemata and especially in exanthematous typhus (typhus fever), further, in relapsing fever, in pneumonia, in severe malarial fevers, in plague and in other severe febrile diseases, and, finally, also in some acute cases of poisoning. On the other hand, it is absent in the milder forms of enteric fever, and also, as a rule, in the severe cases, if they have been properly treated from the onset. This symptom-complex, therefore, which was formerly looked upon as the most important one, has lost its significance, especially in the diagnosis of typhoid fever. But it is not entirely without some diagnostic value. In cases in which a *status typhosus* is present, we may conclude that the patient has been subjected for some time to the action of a high continued fever or that we are dealing with a severe intoxication.

¹ Compare the note p. 16.

In the majority of cases, in practice, we must do without the determination of typhoid bacilli, nor have we pathognomonic symptoms at our command; in cases that are at all developed the diagnosis can still be made without difficulty. This is, however, only true with the proviso, that the individual case is examined carefully and can be accurately observed. If this is not possible, for example, if a patient suffering from a well-advanced affection is seen but once and a reliable report of the previous course of the affection cannot be obtained, a positive diagnosis may be difficult or even impossible, provided the demonstration of the specific bacilli is not possible or the agglutination test cannot be made. In the undeveloped cases of typhus abdominalis levis frequently the diagnosis can be made without difficulty; but there are individual cases in which doubt remains, especially the differentiation from other forms of infections, gastric and intestinal catarrhs, and this may only become possible by the demonstration of bacilli or by the agglutination test. In general, as is true in all diseases, the diagnosis is less facilitated by the search for individual symptoms, which may save the physician a careful examination and if possible render reflection unnecessary, or by the enunciation of individual dogmatic rules which the inexperienced do not understand how to utilize, whereas the practiced physician does not need them, than by the endeavor to separate the necessary from the unnecessary, the important from the unimportant, to differentiate frequent phenomena from rare; in general, by a study of the morbid process in which the memory is burdened less than the recognition of the connection of the individual phenomena as far as is possible. In the individual case careful examination and observation is the most certain method in protecting us from mistakes.

Among the conditions which determine the diagnosis, primarily the *course of the disease* must be considered: Gradual onset with a prodromal stage, slow and gradual rise of the fever, long-continuing febris continua with moderate morning remissions, finally, a transition into an intermittent febrile stage. In cases which have not been observed from the onset or that have not received treatment, a well-developed status typhosus may be of importance, as it points to the fact, that for some time a high degree of fever has been present. In regard to the course of the fever in the individual case, numerous varieties may occur, but, as a rule, the fever curve is characteristic. Only exceptionally, does it occur that the disease begins suddenly, the fever following a chill, rising rapidly and attaining high ranges; such cases usually take a short abortive course, but this must not be counted upon with certainty, as occasionally a prolonged and severe course of the affection may also follow.

Of a special importance in diagnosis are the *abdominal* symptoms, the *enlargement of the spleen* and the *eruption*. Of these phenomena, any one may be absent or escape observation, without on this account excluding enteric fever; the greater the number of these symptoms present, the more certain is the diagnosis. It hardly need be mentioned that these individual symptoms, especially abdominal disturbance or enlargement of the spleen, or even an eruption resembling the roseola of typhoid fever, may also be due to other causes, and for this reason, in the utilization of these phenomena, a certain amount of caution is necessary.

The abdominal symptoms are due to the changes which occur particularly

in the lower portion of the ileum. In the majority of cases diarrhea is present, with fluid "pea-soup-like stools." Upon standing these stools develop layers. It may, however, also occur, that the fluids exuded in the lower part of the small intestine become reabsorbed in the large intestine, and then the diarrhea may be absent temporarily, or even during the entire course of the affection. In such cases, it is of importance to observe that, upon pressure a palpable and often audible *gurgling* may be produced in the ileo-cecal region, proving the presence of large quantities of fluid in the ileum. Further, there is *sensitive-ness upon pressure in the ileo-cecal region*. The belly is tympanitic and, in the later stages of the disease, a milder or severer degree of *meteorism* may be present.

Enlargement of the spleen occurs during the first week and continues to the termination of the affection. In convalescence, so long as the spleen has not returned to its normal size, the possibility of a relapse must be considered. The enlargement of the spleen is absent exceedingly rarely; perhaps in cases in which older perisplenetic adhesions have given rise to a very firm unyielding capsule, these having enclosed the spleen, this may happen. It occurs more frequently that, as the result of marked tympanites, splenic enlargement cannot be recognized.

The appearance of the *eruption* (roseola) usually begins at the end of the first week or early in the second week. It consists of small red spots which usually are somewhat raised above the surface of the skin (*roseola papulosa*), disappearing completely upon pressure with the finger. The eruption occurs in repeated crops, it is noted particularly in the upper abdominal region, upon the chest and upon the back. Only in the fewest cases is the eruption markedly distributed, showing many papules; usually the individual crop is not numerous; it may even be absent entirely or so slightly developed that it is readily overlooked.

The demonstration of a *catarrh of the finer bronchi* is of secondary importance in diagnosis; it is frequently present, but may also be absent in some cases.

The *condition of the pulse* has some importance: So long as cardiac weakness is not present, the pulse frequency is less than in most other diseases that develop a similar high temperature. Besides this, it should be noted, that usually after some duration of the fever, the radial artery is soft and flaccid, easily compressible, and that dirotism is developed markedly enough to be recognized even by the unpracticed finger. It is also worth noting that, whereas in other febrile diseases *the number of the white corpuscles* is often increased above the normal, in uncomplicated enteric fever usually a slight decrease can be noted.

It is essential, in order to determine the diagnosis with certainty, to examine every patient carefully and to exclude all diseases which, upon superficial observation, show a similar clinical picture. In omitting to examine the thorax, a pneumonia or even a phthisis florida may be confused with enteric fever. But, even upon careful examination mistakes are possible. Repeatedly cases of *ptomain poisoning* arising simultaneously in large numbers, have been looked upon as epidemics of typhoid fever. The differentiation is made by the etiology and, as a final resource, by a bacteriological examination and

by the agglutination test. The differentiation from *acute miliary tuberculosis* appears to be particularly difficult, and there are practitioners that are of the opinion, that mistaking one disease for the other, can scarcely be avoided, in the majority of cases. This may be true for those who lay especial stress, in the diagnosis of enteric fever, upon the status typhosus and who look upon the severe cerebral phenomena in a tubercular meningitis, for typhoid symptoms. But, especially in those cases in which meningitis is present, a confusion with enteric fever should not occur; it will not escape the careful observer that in such cases the cerebral phenomena are not simply due to the fever which is present or that which has preceded. Acute miliary tuberculosis may more readily be confounded with enteric fever in those rare cases, that run their course with a high and long-lasting type of continued fever, without a well-developed meningitis, and in which the typhoid symptoms present are only actually dependent upon the fever, and all the more so if, as the result of an especial localization of the tuberculosis, enlargement of the spleen and abdominal symptoms are present. In such cases a conspicuously irregular course of the fever, a greater frequency of the pulse from the onset of the affection, may be suspicious. Frequently, the determination of an old tubercular focus or, in well-developed miliary tuberculosis of the lungs, the existence of conspicuously severe and well-distributed phenomena of catarrh of the finer bronchi, with especially marked dyspnea, may point to the correct diagnosis. In individual cases the ophthalmoscopic proof of miliary tuberculosis in the choroid is decisive. On the other hand, a well-developed typical eruption would decide in favor of enteric fever. Finally, it must be remembered, that although very rarely, acute miliary tuberculosis appears as a sequel of enteric fever. Regarding the differentiation from *typhus fever*, besides the absence of the abdominal symptoms, the rapid rise of the temperature and the other peculiarities, the epidemic conditions are determining. At the onset it may be difficult to recognize the prodromal fever from a beginning attack of variola, or of scarlatina, or of an insidiously beginning pneumonia; usually, however, the differentiation is easy. The affection may be further confounded with malaria, influenza, simple and epidemic meningitis, endocarditis, especially with malignant endocarditis, further with pericarditis, pleurisy, septico-pyemia in its various forms, especially with puerperal fever, further with trichinosis, anthrax, even with uremia and other morbid conditions. How the differentiation is to be made from these diseases, does not require explanation for the practiced physician; only the general remark may be added that we will be the better guarded from mistakes, here as elsewhere, and with greater certainty, the more we reflect upon the possibility of error. Especial difficulties may occur in rare cases, in which the localization of the exciting factor at the onset, occurs in the lungs, or in the kidneys, so that besides the symptoms of a pneumonia, or an acute nephritis, the phenomena on the part of the intestines are less prominent; these are the cases which have been aptly designated *pneumotyphoid* or as *nephrotypoid*. With this it may occur that, only in its further course, the true nature of the disease will be recognized.

Of secondary importance in the diagnosis are the circumstances which, a priori, cause the presence of enteric fever to be more or less likely. During an *epidemic* it will be quite proper to designate an affection as typhoid fever,

rather than at other periods or in other districts in which enteric fever rarely occurs. If the possibility of an infection with the typhoid poison cannot be proven in a patient, the objective phenomena must be very clear if we desire to diagnosticate enteric fever; if, on the other hand, a patient comes from a house in which, simultaneously or previously, well-developed cases have arisen, the case may with great probability be designated as etiologically identical with typhoid fever, even if the objective phenomena are but poorly developed. Further, in the case of an aged person, a tubercular individual, one suffering from cardiac disease, a woman well advanced in pregnancy or one in the puerperal condition, again, a person who has previously passed through an attack of typhoid fever, although in all of these individuals enteric fever may occur, the diagnosis of enteric fever will be made less readily than in a youthful individual.

Finally, in certain cases, special complications or sequels which are particularly frequent in enteric fever may be a support to the diagnosis. *Epistaxis*, for example, is not without diagnostic value. In a later stage, intestinal hemorrhage, perforation, and, to a limited extent, the various complications on the part of the lungs may be important; protracted convalescence, the bodily and mental weakness which is of long duration, alopecia, etc., are of importance. Naturally, all of these phenomena, which may be explained in various ways, are to be utilized with caution, and the utmost attempt must be made, in each individual case, to clearly determine what has been proven by the individual phenomena or has become likely. In cases that are not well developed, which still give rise to doubt in regard to the diagnosis, it may be that the later appearance of a relapse, in which more distinct symptoms appear, will unravel the nature of the affection. Certain other conditions make the presence of enteric fever improbable. Among these, above all, may be mentioned an acute nasal catarrh which, according to experience, does not occur in enteric fever. Herpes labialis vel facialis is against enteric fever, although not with absolute certainty. On the other hand, stomatitis and a catarrhal angina are comparatively frequent at the onset of enteric fever.

PROGNOSIS

As the diagnosis, so also has the prognosis in enteric fever undergone not a few changes in the last half of the previous century. The older physicians were of the opinion, that prognosis in enteric fever was almost impossible. Their principle rule consisted in: "*Spera infestis, metue secundis.*" In fact, the conditions in an affection which shows such manifold characters upon which the prognosis depends are so varied, that for this reason prognosis belongs to the most difficult tests, the solution resting upon the correct weighing of very numerous circumstances. Further, it must be acknowledged from the onset, that an enteric fever patient, even with a favorable course, is in greater danger than a healthy person, in that even in the mildest cases or in those that have apparently run their course, severe conditions may arise late in the disease, for example, perforation of the bowel. But the physician is not supposed to be a prophet: he is not expected to foresee the unusual, but only the usual conditions. And in this respect the better

insight regarding the connection of the various phenomena, which we have acquired in the latest times, has so increased the certainty of prognosis in enteric fever, that in direct contrast to the views of the older physicians we may say: Among the acute diseases, that are dangerous to life, there is scarcely any other, in which the prognosis may be determined with so high a degree of probability, as in the case of enteric fever.

Besides the severity of the affection, which varies greatly in the special case, of great importance in the prognosis is the *individuality of the patient*, as his power of resistance regarding the disease depends upon this. Among the special conditions which must be taken into consideration there are some few, the influence of which have become known by experience.

First, as regards the *age* of the patient. Apart from children under one year of age, we may say that upon the average, the danger is the greater the more advanced the patient is in years. The most favorable age is below fifteen years. On the other hand, in patients over forty years the mortality is markedly greater than the average. This is the more conspicuous, as in younger persons the temperature curve, as a rule, runs a higher course than in older individuals; but this is more than compensated for, by the fact, that younger persons have a much greater power of resistance, and especially that the heart can endure more.

Of great influence in the course of the disease is the *constitution* of the patient, and especially the circumstance, whether he be fat or thin. Obese individuals in enteric fever, as well as in other febrile affections, are in decidedly greater danger. In them the fever upon the average reaches higher grades; and the therapy gives less favorable results, in that the thick adipose covering hinders the artificial cooling of the body. To this may be added, that obese persons have a much lessened power of resistance: Parenchymatous degeneration of the organs occurs earlier, and is more developed, and especially does the heart suffer earlier. Enteric fever is best borne by muscular individuals; and even in anemic or poorly nourished or chlorotic persons the prognosis is more favorable than in the obese.

A conspicuous diminution of the power of resistance is shown by the *habitual users of alcohol*. It is true, in these individuals upon the average the temperature runs a lower course, but, in spite of this, the disturbances are just as well developed and for the most part are just as severe and more dangerous than they are ordinarily. Especially the parenchymatous degeneration of the organs, the onset of which frequently has been previously present, usually develops more quickly into a dangerous condition and especially is the heart less capable of resistance.

Pregnant women and those in the puerperium, if attacked by enteric fever, are in great danger. In the former, frequently abortion or premature labor occurs.

The prognosis is rendered unfavorable by most of the *chronic affections* which are simultaneously present with enteric fever. Affections of the heart are especially serious on account of the danger of paralysis of the heart. This is equally true of emphysema, although, upon the average, the fever curve is lower. Further, patients are in great danger that suffer from chronic catarrh of the finer bronchi, patients with tracheal stenosis the result of

goitre, and, finally, patients affected with pulmonary tuberculosis. In the latter, even if they do not succumb to enteric fever, the pulmonary affection becomes developed to a much greater degree. Patients, the subjects of diabetes mellitus, show fewer disturbances when attacked by enteric fever, and the phenomena due to the rise in temperature are less developed; in them, however, the prognosis is very unfavorable.

In persons that are attacked for the *second time* with typhoid fever, upon the average, a milder course is to be expected.

Of decisive importance for the diagnosis is the *degree of* infection and the severity of the symptoms depending upon this. In this connection the greatest differences arise. There are undeveloped cases that during their entire course only show moderate fever and but few developed morbid phenomena: *Typhus levis*, and beside these others, in whom in the first week the fever and the other symptoms are very severe, in whom, however, early in the course of the second week the fever declines and the affection terminates rapidly: *Abortive typhoid*. These undeveloped cases show a good prognosis throughout, in case unfavorable individual conditions are not present. In cases which run a mild course, at first a severe complication or relapse may arise, this markedly altering the prognosis; and even in mild cases the possibility of an intestinal perforation or of another dangerous complication can not be excluded with certainty. But such occurrences are far more rare in a mild course than they are in severe cases.

The most important support for the determination of the severity of the infection and of the danger is given by the *condition of the fever*. Primarily of importance is the absolute height of the temperature. A simple statistical collection¹ of numerous cases shows that the mortality is the greater, the higher the absolute temperature. Of more importance, however, is the *duration of the rise of temperature* and especially the *duration of the continuous fever*. With every day that the temperature retains its high range without interruption, the danger to the patient grows. The maximum of the temperature, and especially the duration of the fever, can naturally only be ascertained after the disease has run its course; and thus the determination of the dependence of the prognosis upon the height and duration of the rise of temperature would be of questionable value if only the material for this observation could be obtained after the disease had run its course. There are, however, in the primary stages of the affection, certain points of support, which allow us to judge with great probability, the acme and the duration which the temperature will attain. Regarding the height of the range of the temperature which is to be expected during the course of the disease, the fastigium of the temperature which is reached towards the end of the first week is decisive; as a rule, in uncomplicated cases, even in the further course of the disease, the temperature does not go beyond this point. The duration of the fever which is to be expected is denoted to a certain extent by the onset of the disease. The more suddenly the temperature has risen, and the more rapidly in the course of the first week the temperature rises, the sooner is a brief or

¹ Compare *Liebermeister in Ziemssen's Handbuch*, Leipzig, 1876, ii, 1, 2te. Aufl., p. 145; Leipzig, 1886, 3te. Aufl., p. 182.—*G. Doerenberger, Zur Therapie und Statistik des Abdominaltyphus*. Dissertation, Tübingen, 1901.

even an abortive course to be expected. An important sign of the prognosis is given by the observation of the *daily variations* of the temperature. In general, the prognosis is the more favorable the greater the daily variation. A fever which, at the end of the first week and in the second, shows but a slight variation in which, for example, the difference between the maximum and minimum is scarcely a degree and a half F. or less, is very much more rapidly destructive to the organism; on the other hand, a longer duration is to be expected and a much greater tenacity, hence much greater resistance will be offered to our therapeutic procedures. As the morning remissions become more marked and the extent of the normal daily variations is exceeded, the danger which depended upon the fever disappears; and, therefore, the early appearance of marked morning remissions is a favorable omen, as well as an unusually decided remission of the fever, which may occur but once, since this indicates that the fever is less tenacious. And in this connection, the action of the antipyretic treatment is of great importance. The greater the temperature fall, after cold baths, and the longer the period until the previous height is regained the less resistant is the fever, and a milder course is to be expected. Important, in this connection, is also the degree and duration of the remission which is brought about by the action of an antipyretic drug in moderate doses, and to a certain extent it may be looked upon as a reagent from which we may conclude the degree and tenacity of the fever; the prognosis may partly be made to depend upon this. Naturally, it is obvious that the remissions which occur as the result of a marked intestinal hemorrhage, or which appear in the form of a collapse after an intestinal perforation, are not to be regarded as favorable and as belonging to this category; but these accidents are so serious in themselves that in comparison to them such a transitory advantage as a fall in temperature is not to be considered.

Of decided influence upon the prognosis is, further, *the power of resistance of the patient*, which in individual cases, even apart from what has been previously mentioned, shows quite marked peculiarities. Above all, the condition of the *cardiac activity* is one of the most important prognostic signs, and the observation of the pulse under some circumstances may be more important than the temperature. As has already been mentioned in the diagnosis as long as the heart remains strong in enteric fever patients, the frequency of the pulse is apt to be less than in similar febrile conditions which show high temperatures. As long as the frequency is but moderately increased and the pulse is strong, there is no present danger from this point, even if the increase in temperature is prolonged and quite considerable. But it must be considered, that if the necessary precautionary measures are neglected, the scene may rapidly change and it may then be too late. If, on the other hand, the pulse frequency has attained a marked height, if it reaches 120 or more, this is usually an indication that a dangerous cardiac weakness is already present or is impending. Such an excessive increase in pulse frequency is less dangerous if it occurs in a person that has not yet reached adult age, or arises in a very nervous, easily excited woman; it is of less importance if it is only transitory, and especially if we know its particular cause. It is the more serious, the weaker the pulse at the same time, and the greater the symptoms of cardiac weakness, such as hypostasis of the lungs, slight cyanosis, collapse phenomena,

excessive differences between the internal temperature and the temperature of the periphery, or if pulmonary edema is superadded. A statistical collection of the cases, according to the high pulse rate which has been recorded, shows that the mortality increases to an extraordinary degree with the height of the pulse frequency.

Individual patients react very differently in regard to the *cerebral functions*, and this variation has materially assisted in bringing about the result, that the dependence of the psychical disturbances upon the temperature, which are so obvious to the unprejudiced observer, was so long unrecognized. But we must remember that other conditions also, which act upon the cerebral functions, give rise to similar and frequently even greater variations, such as, for instance, the action of alcohol and narcotic poisons. In general, the severe disturbances of the cerebral functions occur particularly in the grave cases, and the danger grows in rapid proportion to the gravity of the psychical disturbances. Other brain symptoms, which are not dependent upon the rise of temperature, which are due to the toxins or to the *special localization* of the cause of the disease, or are due to accidental *complications*, render the prognosis unfavorable. Of especially grave import are meningeal symptoms, further, apoplectiform attacks, epileptiform, or generally distributed convulsions. Less dangerous are melancholic conditions or other well-developed forms of disease of the mind, which occur during the course of the affection or arise during convalescence. But even phenomena, which in the healthy person would be declared to be hysterical, are more marked if they occur at the acme of a somewhat severe enteric attack, rendering the prognosis more unfavorable. If, therefore, it is unquestionable that the variety and gravity of the cerebral phenomena are of great importance in prognosis, we, nevertheless, must be very guarded in attaching too great weight to them, and in so doing neglect other factors. The uncertainty of the prognosis, which was emphasized by the older physicians, was in a large measure due to the circumstance, that the severity and danger of the individual case was judged too much by the development of "typhoid phenomena."

Finally, the prognosis is influenced, to a marked extent, *by the treatment*. Anyone who has had experience in the observation and judgment of the fever treated by antipyretic modes, may give a more favorable prognosis in his cases than the one who undervalues the importance of the fever and expects results alone from an expectant and dietetic, or from an exclusively specific and antitoxin treatment. Whereas in former times the mortality of enteric fever amounted to about 20 per cent. and in some localities was even higher than this, this figure has declined to but a few per cent. among those that use a systematic antipyretic treatment in the cases that come under observation early, so that the lethal outcome of the disease may be looked upon as exceptional and is only especially due to unfortunate complications.

Among the *complications* and *sequels* which render the prognosis unfavorable to a high degree, we shall only mention those which are in close relation to the intestinal lesion.

Extraordinarily dangerous is *perforation of the bowel* which occurs in from 1 to 2 per cent. of the cases, mostly in the severest cases; it appears to arise particularly in patients who come under treatment late in the course of the

disease, especially if they have been walking about or at work early in the disease, exceptionally it may occur in cases which, if severe complications had not occurred, would have been reckoned as among the milder cases. In the majority of cases in which perforation occurs, death takes place usually in the course of the next four days; weeks may, however, pass before the fatal termination takes place, and in some few cases recovery may even result. *Acute peritonitis* without perforation also belongs to the dangerous complications.

Intestinal hemorrhages are frequent in enteric fever and occur particularly in the severe cases. Slight bleeding, as for instance, the appearance of some hemorrhagic mucus or the presence of pure blood, is not serious, in so far, as they do not indicate the future occurrence of severe hemorrhages and prevent the carrying out of a systematic bath treatment. Large hemorrhages must be judged variously according to circumstances. It is exceptional for a person to succumb immediately following a hemorrhage. In a prognostic respect, it is of great importance at what stage of the disease hemorrhage occurs. If at the end of the third or in the fourth week a large intestinal hemorrhage appears, it may occur that the marked falling temperature combined with it will have a favorable influence upon the enteric phenomena present, recovery steadily advancing from that time on. These are the cases which have led competent observers (Graves, Trousseau) to maintain that intestinal hemorrhages are by no means unfavorable in enteric fever, but are rather of favorable prognostic import. A large intestinal hemorrhage, during the earlier course of the disease, is always dangerous; it powerfully diminishes the resistance of the patient and, if a long stage of continued fever follows, the hope that the patient will endure until the end of the affection is greatly diminished, all the more, as the occurrence of an intestinal hemorrhage contraindicates the active treatment by systematic cold bathing.

In some few cases the intestinal ulcers do not heal in the ordinary time, but exist as slowly healing ulcers for some time. They may even, after apparent complete recovery, lead to perforation. Occasionally they keep up a continued mild febrile reaction which, in some cases, may cause grave marasmus and be the final cause of a fatal termination.

Of other complications not connected with the intestinal affection, which are especially frequent and dangerous, those on the part of the lung, must be mentioned. Most of the other complications and sequels render the prognosis more unfavorable. They are, however, so extraordinarily manifold and varied that only an accurate description of them individually would be of value, and a general description of their prognostic importance is impossible.

III. TREATMENT OF ENTERIC FEVER

By F. KLEMPERER, BERLIN

Prophylaxis.—In beginning this chapter, it may be well to say a few words regarding prophylaxis. Prevention of the disease precedes treatment and is also of more importance.

In describing the etiology of enteric fever we saw that water was its chief distributor; we recognized the connection of epidemics with water-supply and water-conduction, which were infected on account of porous cesspools or as the result of faulty canalization. Here prophylaxis is of primary importance. The *supply of good drinking water* is preeminent; of no less importance is the proper hygienic distribution and proper disposal of sewage. Both are in charge of *public hygiene* and still a further part of the prophylaxis of enteric fever is relegated to it, the *inspection of the food-supply*, especially of the milk. Finally, the improvement of *conditions of living* in general, the improvement of the mode of living of the population which hygiene attempts, also have their part in the prevention of enteric fever, especially of its epidemic distribution.

All of these points need not be entered into here. Not that they are not of importance to the physician—the Public Boards of Health cannot do without the assistance of physicians in these labors—but in general they are beyond the sphere of action of the practitioner and are in the hands of Medical Bureaus of Health.

On the other hand, entirely within the power of the individual physician, is another not less important point of the prophylaxis, that is the *prevention of infection from case to case*, the care that the first sporadic case shall not be the starting point of numerous other ones, or even of an epidemic. The source of all infection is, as we have previously described, primarily, always and exclusively, the human being ill of enteric fever—from his dejecta alone the germs of typhoid reach the water, food-substances, etc. To block this source is the duty of the physician. It is his duty to see to it that the germs which come from the patient are destroyed. Above all, the stools of the patient, further, his urine, then the water used in the bath, eventually the expectoration, pus from abscesses, and other products of disease are to be thoroughly *disinfected* before they are thrown away.

Disinfection of the Stools.—To disinfect the stools, lime is most suitable. Sufficient milk of lime is thrown into the bed-pan to cover its floor. After defecation an equal amount of milk of lime is added to the feces, well shaken up, and *allowed to stand for an hour*. The mixture must be decidedly alkaline. The milk of lime is to be freshly prepared. Undissolved calcium is put into stone jars or wooden buckets and as much water is added as will be taken up; the dissolved calcium is to have four times its amount of water added.

(If chloride of lime is used the amount of the same must be 1 per cent. of the urine-fecal mixture. It may be used as a powder or about 20 grams of chlorinated lime with 100 of water may be used. After thorough mixing the stool need only stand for fifteen minutes.)

The *urine* together with the feces or alone may be disinfected by the addition of milk of lime, carbolic acid, or corrosive sublimate. To disinfect the sputa, the pus, etc., lysol, lysoform, formalin, etc., are more useful.

The *bath and wash water* of the typhoid patient, which is not infrequently contaminated during its use, often contains numerous typhoid bacilli, as has been demonstrated. Its disinfection is therefore necessary; unfortunately, on account of the difficulty and cost, this is often neglected. Disinfection may be accomplished by milk of lime (6 litres to a bath of 300 litres), by chlorinated lime (250 grams to 200 litres of water, allowed to act for half an hour—Babucke¹), or by carbolic acid. Corrosive sublimate should not be used if metal tubs are employed.

¹ Centralbl. f. Bakteriöl., Bd. xxvii, 1900.

Water-closets and privies, into which the typhoid dejecta are emptied after their disinfection, should have a plentiful supply of milk of lime and should be thoroughly cleansed. In cleaning the bed-pans, urine glasses, etc., the external surfaces of these glasses should have especial attention, particular care being given to those places at which they are grasped.

Next to the dejecta, the bed clothes of the patient (bedding, underwear, including handkerchiefs, towels, serviettes, and bathing towels, etc.) require especial care.

These immediately after use—before they leave the sick-room—are to be placed in vessels that can be closed, which are filled with a 3 per cent. solution of carbolic acid or enclosed in a sheet that is moistened with a 1 to 20,000 solution of corrosive sublimate, and packed in tight, moist sacks. They must then be disinfected by boiling (in soap-water with the addition of soda or in petroleum soap-water—2 buckets of water to 250 grams of soap and 2 spoons of petroleum—the best method is to take them to an institution in which they can be sterilized) *before they are sent to the laundry*.

The patient is to be washed several times a day, especially the face and hands; after each movement of the bowels these parts are to be thoroughly washed so that the bacteria cannot adhere to them. In spite of the fact that the “cleanly washed body of the typhoid is not contagious” (Gerhardt),¹ every one that comes in contact with the patient is to be exceedingly careful. Those who are constantly busy about the patient, relatives and nurses, are to be emphatically told: That all substances which are utilized in the service of the patient are only to be used by him and by no one else; that in the sick-room no one is to eat or drink outside of the patient; the remains of food which come from the sick-room are to be destroyed; those that enter the sick-room are to have an especial covering for their clothes (linen gown, apron), and those that leave it are to thoroughly disinfect their hands, especially before they leave (with soap and a brush, alcohol and corrosive sublimate).—After the disease has run its course, the sick-room, bed, etc., are to be thoroughly disinfected. If all these precautionary measures are actually followed, it is as good as certain that the individual case will not give rise to others. If, in spite of this, enteric fever in large cities never disappears entirely, and during the favorable season still shows quite a distribution, it is due to the fact that numerous cases until late (in the second week or even later), others because they are so mild, are not recognized as enteric fever at all; but on the other hand, it is also due to the fact that the carrying out of all these prophylactic measures is combined with extraordinary costs and labor, which can only be applied under especially favorable circumstances. This leads to the opinion that enteric fever cases, in so far as is at all practical, should be treated in hospitals. The best interests of the relatives, and of the public at large is served with this, but also the interests of the patient himself, for as the prophylaxis, so does also the treatment and care of the enteric fever case require measures which can only be utilized in the household of the well-to-do. In this connection it should be mentioned that the *transportation* of the patient, even to some distance, in the first two weeks of enteric fever, according to experience, has no serious consequences for the patient.

¹ C. Gerhardt, Die Therapie der Infektionskrankheiten. Bibliothek von Coler, 1902, Bd. x, p. 93.

The question of the *isolation* of the enteric fever patient has been much debated. That the well are to be kept away as much as possible may be gathered from what has been previously said. Especially in schools, armories, prisons, etc., strict attention should be paid to this. In our hospitals, in many instances, the typhoid fever patient is not isolated; individual cases are placed between other cases but great care is given to the fact that the nurses who look after them do not come into contact with other patients; upon a large number of cases being present, separate rooms (isolation wards) are used. It is certainly more advisable to isolate every case of enteric fever, and in the newer hospitals, that are more luxuriously furnished, this is usually carried out.

[The doors and windows of the wards in which the enteric fever cases are treated must be protected by fly-screens. The danger of the conveyance of typhoid germs from the feces to milk or other articles of diet is thus avoided. —Ed.]

An important duty of prophylaxis is, finally, to search for the cause of the individual case, especially in instances where numerous individuals are closely housed, such as in schools, prisons, etc.; to determine whence the infection occurs is of great importance; by recognizing the source of the infection, the danger is speedily put aside. If the water is the carrier of the poison of the disease, or even if it is only suspicious, it should be thoroughly boiled before it is used. Public hygiene is especially concerned in carrying out all these matters of prophylaxis in the individual case; for this reason the report of each case of typhoid is required by law, a fact to which I desire here briefly to call attention.

In cases of special danger of infection, for example, during war, where large numbers of troops are collected, *prophylactic inoculation* comes into question. Bacteriologic investigation in this field has already developed a relatively simple and apparently harmless method of preventive inoculation against enteric fever, which was practiced in quite a large number of cases in the late South African war. We shall discuss this method and its results minutely under bacteriological therapeutics (see page 40).

THERAPY

A. SPECIFIC THERAPY

1. Specific-Drug (Abortive) Therapy.—The history of the treatment of typhoid fever is full of specific treatment by means of drugs and methods. Among the oldest in the treatment of typhoid, to which for a long time an *abortive action* was attributed, were *emetics* and *venesection*. Antimony and venesection, which for a long time dominated in therapy of enteric fever, were said to remove the poison of the disease from the body. The latter, longest in use at the beginning of the previous century, under the influence of Broussais, was used in the therapy of typhoid fever to an enormous extent. A patient of Bouilland¹ affected by enteric fever with a simultaneous pneumonia, was bled

¹ Quoted by Murchison. (Die typhoiden Krankheiten, translated by W. Zülzer, Braunschweig, 1867, p. 578.)

profusely six times from the arm, thrice had wet cups, and 60 leeches to the chest and abdomen!

For the same purpose, to drive away the probable cause of the disease which was supposed to be present in the decomposed masses in the intestine, the treatment by laxatives was employed. The method of de Larroque, which was widely distributed in France in the previous century and which was advised by Andral, Bretonneau, Louis and others, is a combination of emetics and laxatives; the administration of an emetic, consisting of tartar emetic, followed by frequent doses of calomel, castor oil or seidlitz water, laxative enemata and cataplasms to the abdomen. Trousseau advised, only at the onset to give a saline laxative consisting of sodium sulphate or a seidlitz powder, later chalk preparations and bismuth or silver nitrate. English authors preferred *constipating measures* without previous laxatives. Murchison, for example, advised astringents if more than 2 stools occurred in twenty-four hours; he especially employed enemata of starch and opium, also of lead acetate.

Unusually numerous are the drugs that have been praised as specifics. Besides the mineral acids, chlorine water, the iodine and mercurial preparations, there are quinine and digitalis, salicylic acid, carbolic acid, sulphurous salts, etc. Every remedy that showed a specific action in another disease or developed an antipyretic or antifermentative property was soon tried in enteric fever; it found adherents and for a time remained in use as a specific, then to disappear until it was resurrected when it again came into prominence. To quote an example—iodine—the antifermentative action of which had been known for some time, was advised repeatedly in 1840 by Sauer, as iodide of potassium; later by Magonty, 1859, as a potassium iodide solution in France, and then again in 1866 by v. Willebrand in Germany. Murchison in 1867 was entirely opposed to Magonty's method, and in 1876 Liebermeister maintained that it was the only remedy that showed a specific action in enteric fever outside of calomel. The number of cases upon which Liebermeister based his conclusions, was 239; these he had treated with iodine, giving a mortality of 14.6 per cent., compared to 377 cases without specific treatment, with a mortality of 18.3 per cent. Now it is generally known to-day that such, and even very much greater, variations occur in the mortality of enteric fever even without any drug action, and iodine—that was, in fact, later dropped by Liebermeister; in a report of enteric therapy from the Tübingen clinic, in a dissertation¹ in the year 1901, it was no longer mentioned—has disappeared entirely to-day from the treatment of enteric fever, as well as all the other previously mentioned so-called specifics.

Only one drug has retained a certain prominence to-day, which was mentioned besides iodine, namely *calomel*; it was originally used as an antiphlogistic measure on account of the inflammatory nature of the intestinal lesion, later more on account of its purgative action. Advised by Lesser, Wolff, then Schönlein, Traube, and Wunderlich as an abortive treatment for enteric fever, this drug in later times found a convincing advocate in Liebermeister. Liebermeister practiced the CALOMEL TREATMENT in the following manner: He gave three to four doses, each containing one-half a gram ($7\frac{1}{2}$ grains) in twenty-

¹ G. Doerenberger, Zur Therapie und Statistik des Abdominaltyphus. Dissert. Tübingen (Franz Pietzcker), 1901.

four hours, in every case of enteric fever that came under treatment before the ninth day of the disease; in 1876 he wrote regarding its success: "I have now, after having treated over 800 cases in this manner, every reason to continue this method of treatment and to advise it. By the administration of calomel in a sufficiently large number of cases, the duration of the disease was decidedly shortened and its intensity diminished."

Besides Liebermeister, Ziemssen, although less pronouncedly, was in favor of the use of calomel; other clinicians (Bäumler, Curschmann and others) did not advocate its use.

An apparent support was given to calomel during the bacteriological era by the discovery of the disinfecting power of corrosive sublimate. In the administration of calomel, corrosive sublimate forms in the intestine, calomel was therefore looked upon as a powerful *intestinal antiseptic*. The continued investigations regarding the so-called intestinal antiseptics have shown, however, that no remedy, neither calomel, which was known of old, nor the numerous new preparations such as naphthalin, salol, dermatol, formaldehyde, etc., which were all similarly employed in enteric fever and now and then even are recommended as specifics, actually bring about a disinfection of the intestinal contents. In the dose in which these remedies are tolerated in the intestine, they scarcely act in the inhibiting development, not to speak at all of the destructive action that they have upon bacteria in the intestine. The so-called internal antiseptics do not produce a diminution of intestinal germs which is at all worthy of consideration; however, such a condition does arise—as has been proven by exact bacteriological investigation—by purgatives, which evacuate innumerable germs from the intestine. Whereas we could not admit up to the present an actual antisepsis of the intestine, a disinfection of the intestine by the mechanical effect of a laxative may be considered up to a certain extent. In this sense, as an energetically acting purgative, calomel takes the first place among the so-called intestinal disinfectants. Especially in enteric fever, however, purgatives are of only very limited value, for during the period in which the first symptoms of the affection may be plainly recognized the typhoid bacilli have already for some time invaded the intestinal wall, have collected in the enlarged follicles, and here intestinal disinfectants can no longer reach them, nor can purgatives drive them away.

The position of calomel as a specific or as an abortive measure in enteric fever is, therefore, theoretically not tenable, and also in practice it has been shown that just as many cases of enteric fever run an abortive or mild course with, as without, the administration of calomel. The greatest majority of clinicians, therefore, are opposed to this administration of calomel, especially as calomel is by no means a harmless drug, ptyalism, inflammation of the intestinal wall, and other serious results from the action of mercury having been observed. But it must not be concealed that Liebermeister adhered to this treatment the longest even if his opinion—according to the previously mentioned dissertation in which it says: "A specific value, even if slight, cannot be gainsaid the remedy, a better has not been found as yet"—finally sounds somewhat less confident.

Regarding the administration of chlorine water, of carbolated camphor, of naphthalin, formalin [acetozone.—Ed.], etc., which is now and then

advised in medical journals even up to the present time, I may be brief after what has previously been said. They are absolutely without any specific value and do not influence the causative agent of enteric fever in the organism in any manner, even if they may be of use for special (symptomatic) indications (see page 55) in the individual case. The same is also true of *antifebrile drugs*, which we shall consider somewhat more in detail later on: they are occasionally of great value and have their special uses, but a specific, curative property in enteric fever cannot be ascribed to them, not even to the most valuable of them all, quinin (see page 53). We are not in possession of a *specific for enteric fever*.

2. Etiologic (Bacteriologic) Therapy.—The discovery of the specific cause of enteric fever, in the typhoid bacillus, has stirred up anew the search for a specific remedy against the disease, and, at the same time, has opened up new roads of discovery. Active scientific work in the search for immunity, which bore its first therapeutic fruits in Behring's serum therapy against diphtheria and tetanus, has not been neglected in the case of enteric fever. A great number of investigators—among the first I shall mention Beumer and Peiper, Sanarelli, Chantemesse and Widal, Brieger, Kitasato and Wassermann—have busied themselves with the immunization of animals with typhoid bacilli, and with the healing of the infected animals by immunized serum, and they have determined that the conditions, in general, are the same as in all other experimental infections: It is possible to immunize animals by attenuated cultures, or by smaller amounts (being below the lethal dose) of virulent bacteria to large, otherwise fatal, doses of typhoid bacilli, if the process is gradual, given in increased amounts, and the immunity acquired in this manner, if it has attained a high degree, can be transmitted with the serum of the immunized animal to other animals that have not been so treated; the immunized serum, in sufficient amounts and strength, protects animals that have already been infected, and, therefore, acts in a curative manner. I succeeded in immunizing goats, which are very refractory to infection by typhoid bacilli, by administering larger and larger doses of typhoid bacilli—I increased from 1 cc. of a virulent bouillon culture, administered subcutaneously in the course of months, finally up to 200 cc. injected into the peritoneum—and I was able to demonstrate in their blood serum as well as in their milk marked immunization values; these same conditions were found in experimenting with white mice.¹

The transference of these experiments to man were, and are still opposed to great theoretic difficulties even though the result obtained by Stern,² E. Neisser,³ Chantemesse and Widal,⁴ and others, that by the blood serum of convalescents from typhoid, animals also might be protected from the infection by the typhoid bacilli, a bridge has been thrown between the conditions in the animal experiment and the human disease. The disease brought about by typhoid bacilli is especially, even though not exclusively, a toxic process (see page 3), and the antitoxins of the blood serum may confer protection against this.

¹ Arch. f. exper. Path. u. Therap., Bd. xxxi, p. 364.

² Deutsche med. Wochenschr., 1892, Nr. 37 u. Zeitschr. f. Hyg. u. Infektionskrankheiten, Bd. xvi, p. 458.

³ Zeitschr. f. klin. Medicin., Bd. xxiii.

⁴ Annal. de l'Inst. Pasteur, 1892, 11.

The typhoid disease in man, on the contrary, is primarily an infectious one and curative sera have not shown themselves as especially active when opposed to the non-toxic infectious diseases. But at some time or other the action of the typhoid toxins also plays greater or less rôle in many cases in enteric fever in man—and if serum therapy controls this, its employment would be justified and useful. Then again, the typhoid immune serum of the animal, in Pfeiffer's sense, is bactericidal, it contains the dissolved bacterial (lysigenous) substances which Pfeiffer was the first to discover, in the typhoid immune serum, and these bacteriolysins are transmitted to the human being with the serum. According to Ehrlich's theory, the serum only carries a part of the substances necessary to produce bacterial immunity, the immune body (amboceptor); to produce the immunizing action a second body is necessary, the complement. Whether the complements are present in the human organism, so that the administration of the immune body alone would be sufficient, or whether it is necessary to add to the immune serum the complements (by the addition of human to animal normal serum, as Wassermann advises), this can only be decided by a trial in man. Experiments with the serum therapy of enteric fever, therefore, although the conditions are not so clear or so hopeful as in diphtheria, are justifiable and even necessary; regarding their value or non-value, practical experience in the human being alone can give us light.

Besides some few experiments in the treatment of enteric fever patients, with the serum of typhoid fever convalescents (v. Jaksch,¹ Hammerschlag,² Weisbecker,³ Hughes and Cortes,⁴ and others), we are in the possession of experiments and treatment of immunized animals by Peiper,⁵ Bürger, Silvestri, Spirig and others, and especially by Chantemesse and Widal.⁶ In England a typhoid serum which Bokenham⁷ has obtained from horses, is sold by the well-known firm of Burroughs, Wellcome & Co.; Pope,⁸ Cooper,⁹ Steele,¹⁰ Cowen,¹¹ and others have reported cases treated with this serum. The opinions of individual authors are very different. Some see no especial influence from the serum, and no cause to assume that the mild or smooth course that their cases showed was due to the serum injection. The opinions of others are more decided and more favorable. A few of the English authors note a decided influence upon the fever curve with each serum injection, as well as a noteworthy amelioration of the general phenomena after the injection. Spirig,¹² who utilized the serum manufactured near Häfler (Bern), emphasizes, that with every injection, temperature and pulse fell decidedly. Noteworthy, above all, is the opinion of Chantemesse¹³ as he has had a relatively

¹ Pollak, Zeitschr. f. Heilkunde, 1896, p. 447.

² Deutsch. med. Wochenschr., 1893, Nr. 30.

³ Zeitschr. f. klin. Med., Bd. xxxii, p. 188.

⁴ Arch. f. klin. Med., Bd. xxviii.

⁵ 13. Congress f. inn. Medicin und Zeitschr. f. klin. Med., Bd. xxviii, p. 328.

⁶ Sem. méd., 1893, 1896, 1898, et 1901; Bull. méd., 23. Fév., 1896.

⁷ Pathol. Soc. of London, January 4, 1898. Brit. Med. Journ., 1898, p. 87.

⁸ Brit. Med. Journ., 1897, p. 259.

⁹ *Idem*, p. 518.

¹⁰ *Idem*, p. 970.

¹¹ Lancet, September 16, 1899.

¹² Correspondenzbl. f. Schweizer Aerzte, 1899, p. 385.

¹³ Traité de Médecine, Bd. ii, p. 205.

large experience. This author reported in the year 1899, seventy of his own cases, in which death occurred in four on account of complications. He emphasizes the fact that, he does not wish to draw conclusions from this number, but however, on the basis of the frequent decided action of each injection upon temperature, pulse and general condition, and especially on account of the mild and abortive course of the cases, even of those that were originally severe, he was convinced of the specific curative action of the serum.

In the year 1895, as an assistant of Prof. Naunyn, in the Strassburg clinic, in connection with E. Levy, I treated 5 cases of enteric fever with the serum obtained from a dog (proven to have been effective, showing curative properties in the animal experiment). Regarding our results, we wrote as follows:¹ "The cases showed a *mild* type; whether the treatment had the slightest influence in this respect it is impossible to say. Only this much may be maintained, regarding the serum therapy of enteric fever upon the basis of our few cases, that *the treatment is entirely without danger*, and that it does *not abort* the disease; if it exerts an influence at all, it only shows itself in the fact that the disease runs a mild and rapid course, immunity occurring more rapidly but in the usual manner common to enteric fever with its peculiar febrile curve."

Hence, it can be seen that the results of the various experiments are not uniform, but it must also be remembered that their serum is not a uniform one but originates from various sources having different strength. Perhaps also, the greater prominence of toxic symptoms in the various cases is a factor, as only the antitoxic effect of the injection of serum, according to our views, could be noted in the influence when the temperature, pulse and the cerebral symptoms, the bactericidal (bacteriolytic, antibacterial) action would have to occur gradually and show itself singly in the mild and shorter course of the case. But no matter, it is certain from the experiences that have been communicated up to now, there is surely nothing that is opposed to the continuance of these experiments, according to our opinion there is much that favors it. We should therefore wish that also in Germany—as has already occurred in foreign countries (see above)—a reliable laboratory might be established, that would be able to furnish us with a uniform and powerful typhoid serum. Only by the combined action of larger circles of physicians, in these curative tests, can a decision be rendered regarding the value of serum therapy in enteric fever.²

In connection with serum therapy, I desire to report briefly, a preparation that for some time has been placed upon the market by an unknown manufacturer, and adver-

¹ Berliner klin. Wochenschr., 1895, Nr. 28.

² *Du Mesnil* (the curative serum treatment of typhus abdominalis. Altonaer Aerzteverein, 26. März 1902, Münchener med. Wochenschrift, 1902, p. 1238) reports 6 cases which he treated by a serum which Prof. Tavel took from horses (the Swiss Serum and Inoculation Institute, which is under the control of the State, supplies this). He writes: "In a sufficient dose, 10 to 40 ccm., a step-like form and temperature was constantly observed, even in the first weeks of typhoid, so that it was possible to change the stage of continued fever into steep curves and convalescence by the injections; in keeping with the fall of temperature, the general condition improved, the patients becoming hungry. In some cases, upon the cessation of the injections, rises in temperature with all the signs of a relapse occurred anew, which, by means of injections, could be combated in the previously described manner."

tised in the medical journals under the name Anti-typhoid Extract. V. Jez, a Vienna physician, in 1899 published an article: "The treatment of typhoid fever with the typhoid extract,"¹ which in many respects was very remarkable. In connection with a demonstration of Wassermann's, that the toxins of infectious substances are especially present in the thymus gland, bone marrow, brain, and spinal cord, Jez prepared an alcohol-glycerin extract from the previously mentioned organs of highly immunized rabbits, and treated typhoid patients with this preparation, which he designated "anti-typhoid extract." The results of 18 cases, which he reported, were "unexpectedly favorable": From the beginning, marked remission occurred—fall in the temperature from 39° C. to 36° C.—after but a few days complete apyrexia, the stools lessened in frequency, the general condition improved, etc. Several points in Jez's communications were suspicious, so; especially the announcement that subcutaneous injections of his remedy did not act so promptly or markedly as its administration per os. The report, regarding the production of the extract, was not as accurate as one might expect, so that experiments might be repeated by others. But Jez produced explicit clinical histories and very remarkable fever curves. His reports were bound to produce an impression which was even increased when Eichhorst² in the following year reported favorable results in 12 cases with the anti-typhoid extract, and Jez³ himself, in connection with another Vienna author, lately reported altogether 50 cases more.

This impression was, however, annihilated by an event which was published a year or two ago in the Wiener med. Wochenschrift, and which deprived Jez of all confidence.⁴ An article by Dr. Pometta (Brig) reported favorably regarding Jez's anti-typhoid extract. Some time later Dr. Pometta protested against the misuse of his name: He did not write the article at all, but Jez published it himself upon the basis of a private letter from Dr. Pometta. In Pometta's letter an "impression" was spoken of which was "rather favorable"; in the article which Jez published under Pometta's name, these had become results which were "very favorable." Pometta wrote a letter to Jez, after he had treated 4 cases which ran rather a favorable course. The next cases, however, soon taught him that this was not due to the remedy; after treating 6 cases he declared the action of the anti-typhoid extract to be very questionable, usually it had no effect, it was "by no means a typhoid specific."

Jez, as far as I can learn, has not replied since then; the matter appears to be closed regarding his anti-typhoid extract.

In the last few years a second etiologico-bacteriological treatment has arisen, besides serum therapy, which requires full observation as it is based upon a sound scientific foundation. This consists—in contrast to the passive, indirect, mediate immunization by the serum—in the *active, direct, immediate immunization* of the diseased organism by the attenuated virus of the disease, a process which was lately designated by v. Behring as *Jennerization*. This method of immunization must be considered primarily, naturally, for prophylactic purposes. As a preventive inoculation against enteric fever, it has been recommended in Germany by Pfeiffer and Kolle;⁵ they sterilize a virulent accumulation of typhoid bacilli, at a temperature of 56° C. for two to three hours; this is injected into the human being under the skin of the back. A few hours after redness and swelling appear at the point of injection, as well as malaise and chilliness; this malaise increases, the temperature rises to 102.2° F. and higher; after 24 hours the symptoms improve, upon the third day they have usually disappeared completely. The serum of the inoculated

¹ Wiener med. Wochenschr., 1899, Nr. 8, p. 346.

² Therap. Monatshefte, 1900, p. 115.

³ Wiener klin. Wochenschr., 1901, Nr. 4.

⁴ Wiener med. Wochenschr., 1901, Nr. 28 u. 46.

⁵ Zeitschr. f. Hygiene und Infektionskrankh., Bd. xxi, 1896. Deutsche med. Wochenschrift, 1896.

individual now shows a specific alteration, it proves to be bactericidal (bacteriolytic), mostly, it has also agglutinating properties. According to the investigations of Pfeiffer and Marx,¹ the inoculated material is not damaged in its immunizing action by an addition of 0.5 per cent. phenol, the carbolized vaccine retains its active properties for months.

Whereas in Germany this preventive inoculation for enteric fever has not been utilized in practice, in England the method has gained great importance and distribution for itself in the last few years. Among the English troops in India, the enteric fever morbidity and mortality has always been very great, and in the South African war many succumbed to enteric fever. Prof. Wright in Netley recommended preventive inoculation in all soldiers that were sent to the colonies; he went to India himself and made propaganda for preventive inoculation among the regiments stationed there. Quite a large number of persons submitted to this treatment.

Wright and Semple² had arrived at the same results, independently of Pfeiffer and Kolle, by utilizing the vaccine, which is heated at a temperature of 60° C. from five to ten minutes, for this purpose employing an emulsion of inanimate typhoid bacilli of a twenty-four-hour old agar culture of previously virulent typhoid bacilli. The dose of the emulsion of the living bacilli which would represent the lethal dose for a guinea-pig (a quarter of a tube) is sufficient in the dead condition of the bacilli to represent a strong immunization dose for an adult. After a subcutaneous injection in the same locality, marked inflammation developed, which only disappeared completely after forty-eight hours; the constitutional effect is shown by fever, insomnia, occasionally in collapse-like weakness, which occurs a few hours after injection. The majority of those inoculated—except for the local painful tension and reddening—are quite normal again upon the following day, however, some few remain ill for several weeks. Utilizing smaller doses ($\frac{1}{20}$ to $\frac{1}{6}$ of a tube), the local as well as the constitutional symptoms are very much slighter; but moderate local tension, slight chilliness, with a moderate rise in temperature, restlessness, which disappeared completely after twenty-four hours. Wright assumes that the immunity acquired by a powerful inoculation lasts several years.

Wright's preventive inoculation has been repeated by numerous authors—such as Sir Dyce Duckworth,³ Marsden, Wilson,⁴ Cayley,⁵ and others—and all agree regarding the absence of danger of the method. They advise a smaller dose for inoculation, the consequences of which will have disappeared within thirty-six hours, and that the inoculation be repeated in from ten to twelve days. The reaction after the second inoculation was usually much slighter. Regarding the results of preventive inoculation, it is naturally very difficult to form an opinion. The inoculated persons show markedly increased agglutination values in their blood; this, however, cannot be looked upon as a certain expression of immunity (compare page 15). Only statistics can decide, and thus it is explained that, in spite of quite a number of

¹ Deutsche med. Wochenschr., 1898.

² Brit. Med. Journ., January 30, 1897, p. 256.

³ *Idem*, November 18, 1899.

⁴ *Idem*, April 28, 1900, pp. 1017 and 1018.

⁵ *Idem*, 1901, p. 84.

inoculations—which we owe to the activity of Wright—the numbers are still too small to form a definite opinion. Nevertheless, the results gained up to the present are very remarkable. In one of the last communications¹ regarding the conditions, I find that among 30,353 soldiers in India, 4,502 inoculated ones gave a morbidity of 0.98 per cent., and a mortality of 0.2 per cent. compared to 2.5 per cent. morbidity and 0.56 per cent. mortality among the non-inoculated.²

The opinion is variously expressed, that if the affection occurs in those that have been inoculated it runs a milder and briefer course (Cayley, Wilson).

Some observers, naturally, question the value of the inoculation. Washbourn,³ for example, lost two inoculated patients and does not admit the preventive, or even the attenuating influence of the inoculation. As opposed to this, others call attention to the fact that the majority of the patients were inoculated but once, hence the inoculation was too weak. Nevertheless, the question regarding preventive inoculation cannot be looked upon as closed, but that it deserves our closest attention, and that it deserves further trial, in so far as possible, is beyond doubt, all the more as the inoculation is not only prophylactic but may also be of therapeutic value.

It has been determined by animal experiment that the subsequent direct immunization of the infected organization by bacterial products is possible, therefore, cure by these means is also possible, only provided the infection does not run too rapid a course. Brieger, Katasato and Wassermann⁴ showed, by experiments with erysipelas in pigs, “that in favorably situated cases, those running a subacute course, it is possible by a rapid appearance of immunity, artificially produced by suitably prepared cultures, to abort the pathological process which has already developed.” And even in the pneumococcus infection of rabbits, G. Klemperer and myself⁵ succeeded in attaining recovery by subsequent immediate immunization, provided we were able to prolong the infection by means of attenuation of the pneumococci (growth at 40.5° C.), and if the subsequent immunization was forced by means of large and repeated doses of the immunizing fluid. In human pathology we already have an example of the curative influence of subsequent immunization which, naturally, requires further confirmation. This example concerns variola, the preventive inoculation after Jenner’s method, as is well known, represents the type of a direct, active method of immunization by the modified (attenuated) virus of the disease. Russian authors⁶ have called attention to the fact that a powerful, frequently repeated (twice daily) inoculation for several days (vaccination),

¹ Brit. Med. Journ., September 21, 1901, p. 842.

² The book just published by Marx, *Experimental Diagnosis, Serum Therapy, and Prophylaxis of the Infectious Diseases* (Library of v. Coler, vol. xi, 1902), by which I quote the following figures which Prof. Wright has sent this author regarding the conditions during the siege of Ladysmith. Inoculated, 1,705; cases, 33 = 1.93 per cent.; deaths, 6 = 0.35 per cent. Non-inoculated, 10,529; cases, 1,496 = 13.42 per cent.; deaths, 336 = 3.2 per cent.

³ Brit. Med. Journ., June 16, 1900, p. 1456.

⁴ Zeitschr. f. Hyg. u. Infektionskrankh., xii, p. 175.

⁵ XI Congress f. innere Medicin, Leipzig, 1892.

⁶ N. J. Kotowtschikoff, Ueber die Behandlung des Eiterungsstadiums der Variola vera. Zeitschr. f. klin. Med., Bd. xxxviii, S. 265.

influences the infected and even the already diseased person, that smallpox runs a milder and shorter course. Of all diseases, however, enteric fever should be most suitable for this method of treatment, as in its gradual development and in its slow course there is sufficient time to begin immunization and to increase it to the required extent. In E. Fränkel's¹ communication, experiments have already been attempted in this direction, the results of which do not appear to be unfavorable; they have not been quite confirmed, but nowhere have they as yet been tested with the necessary frequency. Lately there has appeared a remarkable publication by Petruschky² who, assisted by Dr. Freymuth, has followed this method of treatment in the city hospital of Danzig. Petruschky utilized a preparation which he designated typhoin. This preparation simply represented an accumulation of dead typhoid bacilli. The patient received the following injections of this mixture, subcutaneously in the thigh:

1st day, 0.05 cc. in the morning, 0.1 cc. in the evening,
2nd day, .01 cc. in the morning, 0.2 cc. in the evening,
3rd day, .02 cc. in the morning, 0.3 cc. in the evening.

Outside of a transitory redness and painfulness at the point of injection, disagreeable accompanying phenomena were never noticed. Petruschky writes regarding this treatment: In recent and uncomplicated cases of true enteric fever, which come under treatment before the middle of the second week, the severity of the disease has ceased after a three-day treatment; the temperature fell to normal, the pulse rose, the mind cleared. Petruschky gives accurate descriptions, and offers physicians who have an opportunity of observing epidemics, those connected with hospitals, etc., in fact those who have an opportunity of treating large numbers of cases of enteric fever, his culture preparation, which keeps from three to four weeks.

I have dwelt for some time upon the description of these etiologico-therapeutic endeavors, although I know that practically this method of treatment is not quite ready for use, but they represent, at least we may hope so, the therapeutics of the future, as the previously described medico-specific methods of treatment represent the therapy of the past.

It is now time to return to the present, and to describe what we are capable of accomplishing to-day in our treatment of enteric fever. This is not little, in spite of the fact that we do not possess a specific mode of treatment. The rational aim of our treatment is to assure a normal course for the affection, to cause the disease to run its course, and terminate in spontaneous recovery. The most important auxiliary measures of attaining this end are offered by the hygienic, dietetic treatment. The first place in our therapeutics, however, is taken up by

B. NURSING AND NUTRITION

Nursing.—The typhoid patient is to be put to bed as soon as possible, even with the first, still doubtful, phenomena of the disease. According to

¹ Deutsche med. Wochenschr., 1893, Nr. 41.

² Deutsche med. Wochenschr., 1902, Nr. 12.

experience, patients that wander about for a longer or shorter time, show a severer course.

The sick-chamber and the bed are to be arranged with especial care, on account of the length and duration of the affection. The room should be large and airy and as quiet as possible (not one that is situated directly toward the street). There must be sufficient room so that the bed may be reached from all sides; it is better to have two beds (see below), and there should be sufficient space for bathing arrangements. Besides the necessary furniture which is to be utilized by the patient, the room is to be as bare as possible, above all, there should be no unnecessary articles and decorative features that catch and retain dust (looking-glasses, pictures, etc.), with which the patient sometimes busies himself in a very disturbing manner during his delirious moments. The temperature of the room is not to be above 68° F.; the upper windows, eventually those in the adjoining room, may remain open permanently or—in winter—at least for a part of the time.

The bed is to be plain and light: a firm mattress—no soft under bedding—an indiarubber cover and a sheet which is to be carefully smoothed, a cover, and in summer weather, eventually only a linen sheet. The danger of bed-sore is so great that this must always be remembered. In every severe case it is advisable from the onset to use a water-bed, or at least an air-cushion, under the patient. Early in the disease, the patient may remain quietly in the dorsal decubitus. Later, from about the end of the second week on, he is to be changed frequently to the lateral position, varying from left to right. A cautious and careful assumption of the half-recumbent position—which is daily necessary for the examination of the posterior lower parts of the chest—is advisable to prevent hypostatic congestion of the lungs; but the patient is not to raise himself. Even at the onset of the affection and with a mild course, feces and urine are only to be discharged in the recumbent posture. While the patient is carefully raised, the nurse places the bed-pan under him. It is very advisable to have a second bed near the one in which the patient is placed; to this bed the patient may be moved during the times when the other bed is being cleaned or freshened up; this is a great relief to the patient and makes nursing easier.

Absolute quiet is necessary in the sick-room; no unnecessary persons should be allowed to enter. All external impressions are to be excluded from the patient; reading matter, visitors, etc., are to be prohibited even in the mildest cases.

Great importance must be given to absolute cleanliness of the patient. At least twice daily—morning and evening—he is to be thoroughly washed with fresh water and soap, a brush being used for the hands. The soiled parts about the buttocks, etc., are to be carefully cleansed after each evacuation of the bowels; rubbing with spirit of camphor, powder, etc., are best even before signs of impending bed-sore are present. Of no less importance than the absolute cleanliness of the body is the necessity of having clean linen; body and bed linen are to be changed daily, more frequently if soiled.

Especial care is to be given to cleansing of the mouth of the patient. Frequent washing of the same with cool water, brushing the teeth, moistening the dry lips (with cool water, almond oil and glycerin in equal parts) not

only refreshes the patient, but prevents sordes, which is always a sign of neglect. Unquestionably, in this manner many complications on the part of the parotid gland, of the naso-pharyngeal space, the ear, the larynx, etc., will be avoided.

The nursing of the patient during day and night is to be carried on with like care; this of course requires very extraordinary exertion on the part of the nurses, even if there be two in the given case. Only under very special circumstances should the nursing of the enteric fever patient be left to friends or relatives, particularly when there is additional labor in treatment by baths, which require especial knowledge and dexterity on the part of the nurse. After what has been said, it is scarcely necessary to remark, that only in well-to-do families is it possible to treat an enteric fever patient in this manner in his own home, that it is far better for poorer patients, or for those without friends to be sent to the hospital (compare page 33).

Nourishment.—The nourishment, which is an especial part of the therapy of enteric fever, forms a link in the chain, and is immediately connected with the care of the patient. Although the diet belongs to the orders of the physician, its execution is particularly in the hands of the nurses, but, naturally, the physician is to watch and to assist in each detail.

Although the measures of hygiene and nursing of the patient, which have been previously mentioned, serve in a more negative manner by warding off deleterious effects and complications, all points serve one purpose in the treatment, to maintain the strength of the patient and, in this sense, only far more energetically and in a much more positive manner, does nutrition serve this purpose. In scarcely any other febrile disease can a similar importance be attached to nourishment as that in the case of typhoid fever, which weakens the powers of the patient in an extraordinary manner, often leading to a decided loss of the body-substance by the high and long-continued fever. Leyden,¹ in his well-known estimations, puts the loss of weight in typhoid fever in the remittent stage, per day and per kilogram at 3.5 per cent., E. Barth,² showed, that with an original weight of 125 pounds, in twenty-two days of fever, an average loss of 18 pounds occurred.

Regarding the conditions of metabolism in fever and the fundamental principles of the nourishment of febrile patients, Leyden in his article on pneumonia (see Pneumonia) has given explicit directions. I do not desire to repeat what has been stated there, but will only briefly point out that a proper nourishment in enteric fever, as little as in other fevers, is able to cover the entire loss—the portion which is due to the toxic action of the febrile course cannot be prevented—that, however, a very large part may be maintained, namely that which is due to inanition, on account of the insufficient intake of food. And much is gained by this. Even with careful nutrition, the patient is very much weakened after the disease has run its course, but by no means in the same manner and with such a loss of resistance towards all the dangers of the last stages of the disease and of convalescence as was formerly the case when the fever was treated by the withdrawal of nourishment. It is shown by Leyden's¹ tables that even with high fever the typhoid patient need not

¹ Deutsches Archiv f. klin. Med., v, 1869, p. 360.

² Zeitschr. f. klin. Med., Bd. xli, p. 31.

necessarily lose weight daily, that a mild enteric fever may run its entire course without loss of weight, even with a slight gain, in which, naturally, the retention of water during the fever may be partly responsible, but careful nursing and nutrition certainly play the greater part. There can be no question that the improvement in the course and in the termination of the affection in the last decades which has been universally recognized, besides other factors such as the better nutrition which the typhoid patients now have, are mostly responsible.

The nutrition in enteric fever is to be conducted according to the general principles employed in the nutrition of all fever patients, but the special condition of enteric fever, the affection of the intestine, must be reckoned with in this instance. The functions of the digestive tract are generally weakened in fever (see Pneumonia); in all infectious diseases, therefore, the diet is particularly limited to easily digested fluid food, and this must be especially the case in enteric fever, in which the lower part of the bowel is the seat of ulcers, in which the tendency to diarrhea is a general symptom and every irritation of feces-forming food occasions grave dangers. Hence, from olden times the diet of typhoid patients has consisted of drink and fluid food-substances. To this fundamental rule, even to-day, in all severe cases at least, strict adherence is attached. Only nowadays, besides this command, a second equally important one has arisen, that in this fluid diet sufficient nutritive value must be introduced. The requirement of fever patients in twenty-four hours is estimated at about 2,500 calories, which had better consist in 100 grams of albumen, 100 grams of fat, and 300 grams of carbohydrates. These figures are in keeping with theoretical calculations, but the practical requirement is somewhat less than this. Although great value is to be attached to nutrition of the enteric fever patient, it must be observed, on the other hand, that too much food is no less dangerous than too little. It must not be forgotten that the affected intestinal canal requires consideration, that frequent meals unnecessarily tire the patient. The endeavor to nourish the patient as well as possible must not lead to "over-feeding." In general we may content ourselves with a calory supply of about 2,000; this will give us the best medium between under-nutrition and over-feeding.

Regarding the nutrition of the typhoid patient in general, the following may be said: The patient shall have fluids in plentiful amount. Usually stupor prevents the patient asking for drink himself. The nurse, therefore, at regular short intervals—during the day at least each half hour—is to give it to him, a small quantity, however, being supplied each time.

[There are periods of apparently refreshing sleep in which it is better not to disturb the patient so often, even for the sake of administering water.—Ed.]

The total amount of the fluid intake (including the food) in twenty-four hours should amount to $2\frac{1}{2}$ to 3 litres. This prevents dryness of the lips and mouth, and, at the same time—an important object of the treatment—the flushing of the body is accomplished. The amount of urine, as a measure of the sufficient intake of water, which is of importance, should not be less than 1,500 to 2,000 cc. As a drink, cool, clear water, eventually an alkaline mineral water (non-carbonated) should be administered; weak tea or coffee, lemonade, etc., are permitted.

Milk is of most importance among the nutritive substances. This is to be given in gradually increasing amounts, beginning on the first day at $\frac{1}{2}$ litre, and increasing until at the acme of the disease when $1\frac{1}{2}$ to 2 litres are given. An addition of 50 grams of sugar of milk and 100 cc. of cream to 1 litre of the milk markedly increases the nutritive value. If the patient takes about $1\frac{1}{2}$ litres of milk, $\frac{1}{2}$ litre of cream and 100 grams of milk-sugar in twenty-four hours (and besides this some alcohol, see below), his calory requirement is completely covered.

No special stress is to be laid upon the strict division of special meal-times. In general the patient is to have 200 to 250 cc. of milk, bouillon or soup, every two hours, but larger quantities of milk may be divided over several hours. It must be remembered that the patient requires rest, and that, therefore, from time to time, longer pauses must take place between the feedings. Especially at night, a large food-supply is to be given but once, at most twice during the night. It is important to utilize the improved condition of the patient after the bath (see below) to supply nourishment at that time. I shall here, as an example, give the diet list of a typhoid patient treated in Leyden's clinic:¹

C. —, age twenty-seven; seventeenth day of disease; 2 litres of milk, $\frac{3}{4}$ litre of cream, 200 grams of milk-sugar, 200 grams of water, have been prepared for mixture and are placed upon ice and kept at this temperature.

7 A.M.: Temperature 103.6° F., pulse 110; 150 c.c. milk-mixture.

8.30 A.M.: 100 c.c. milk-mixture.

9 A.M.: Bath at 72° to 65° F.

9.30 A.M.: Temperature 100.9° F., pulse 104; 150 c.c. milk-mixture, 50 c.c. sherry.

11 A.M.: Cup of bouillon; soon afterwards fecal movement; 100 c.c. lemonade.

12 NOON: Temperature 103.1° F., pulse 110; until 1 o'clock 150 c.c. milk-mixture taken gradually.

12.30 P.M.: Bath, 72° to 65° F. Temperature 101.8° F., pulse 108; 50 c.c. sherry.

2 to 4 P.M.: 300 c.c. milk-mixture gradually administered (between 1 and 4 P.M. two fecal movements).

4.30 P.M.: Temperature 104.5° F., followed by bath with effusions.

5.15 P.M.: 101.3° F.; 25 c.c. brandy.

5.30 P.M.: 150 c.c. milk-mixture.

6 P.M.: Temperature 103.8° F., pulse 112.

Between 6 and 8 P.M.: 300 c.c. milk-mixture, 50 c.c. sherry.

8 P.M.: Temperature 104.9° F.; bath 72° to 65° F.; effusion; 25 c.c. brandy.

Between 8 and 10 P.M.: 300 c.c. lemonade.

Five hours' sleep after morphia, grains $\frac{1}{6}$. Upon awakening, milk or drink each time; during the entire night 450 c.c. milk-mixture and 200 c.c. lemonade taken.

Total amount of fluid, 2,700 c.c., in which there were $1\frac{1}{2}$ litres milk, about $\frac{1}{2}$ litre cream, 150 grams of sugar-of-milk, 100 grams sherry, 50 grams brandy, amounting to—total amount of nourishment, consisting of 70 grams of albumin, 103 grams of fat, 239 grams of carbohydrates, with 2,265 calories.

Besides the milk, soups consisting of starchy and pappy substances (regarding their preparation and nutritive value, see Pneumonia), and bouillon are to be considered in the nourishment of typhoid fever patients; these may be given from time to time, alternating with the milk. If sufficient milk is taken, these foods are of less importance. It must be especially emphasized,

¹ v. Leyden u. G. Klemperer, Die Ernährungstherapie in acuten Fieberkrankheiten in v. Leyden's Handbuch der Ernährungstherapie, Bd. ii, p. 436.

that a variation in the nourishment, in severe cases of enteric fever, is by no means necessary; the monotony of the food is not at all appreciated by the patients in their soporous condition.

Now it is not always possible to give the patients sufficient milk, not rarely it is not well borne, and is rejected by the patient, giving rise to nausea, sensation of fulness, meteorism and increased diarrhea. The quantity is then reduced—which, however, must never be increased before the previous quantity is well borne—is diluted with water, tea or coffee, and an attempt is made to make it more palatable by the addition of brandy or salt, or of lime water (a table-spoonful of lime water, or a teaspoonful of calcium carbonate or calcium phosphate to a glass of milk), given with cocoa in the form of milk-soup, briefly, everything should be tried before its administration is entirely given up. No other food-substance which may be given to the enteric fever patient, even the best prepared soups, can substitute for the value of milk. The nourishment of the enteric fever patient will always give rise to difficulty if we do not succeed in administering at least 1 litre of milk per day. If this is the case, the patient taking less than 1 litre, or no milk at all, then soups, which must be prepared with especial care, should be given in larger quantities. Instead of simple bouillon, bouillon with the yolk of an egg (also wine with egg) and grits, sago, etc., may be given instead of the simple flour soups, with the addition of beef extract, neutrose, somatose, of some vegetables, and similar preparations. It must, however, be emphasized, that all these preparations are superfluous if the patient takes sufficient milk, and that in no case are they capable of entirely substituting for the milk.

If the milk must be dispensed with entirely, or nearly so—on account of a repugnance which cannot be overcome, on account of vomiting, marked meteorism, or profuse diarrhea—the question arises, whether nutritive substances which are a little more compact, such as soups, eggs, rice, spinach, potato soup, and even softened wheat bread and scraped meat may be administered.

This question is not so unentitled to consideration as we might assume at first sight. Fluid nourishment is advised as the only reliable form, for the reason that it does not irritate the intestine and does not produce peristalsis. But particularly milk, which is recognized as the best food for enteric fever patients, forms lumpy coagula in the stomach, of which about 6 per cent. to 10 per cent., as with other food, is transformed into feces. “From this it certainly follows”—E. v. Leyden and G. Klemperer¹ remark, in describing the nutritive therapy of acute febrile diseases—“that not only fluid and dissolved food is allowable in enteric fever, but that also other nutritive substances may be employed, in so far as they reach the stomach in a very finely divided condition, so that their digestion in the stomach and intestine does not give rise to difficulties.”

Similar reasoning led an English author, A. G. Barrs (Leeds),² a few years ago in arriving at the far-reaching conclusion that enteric fever patients should have compact food early in the course of the affection. Barrs advises that every typhoid patient that can swallow such food at all, should have, from

¹ Handbuch der Ernährungstherapie, Bd. ii, p. 437.

² Brit. Med. Journ., January 9, 1897, p. 125.

the beginning, tender meat, wheat bread and butter, eggs, etc. From the onset of defervescence, however, the usual mixed food is to be given. Barrs reports more than thirty cases that he has treated in this manner; he did not lose a single case, the condition of strength remained, according to Barrs' report, greater than with the usual fluid nourishment. An active controversy arose in English medical journals in connection with Barrs' communication: The majority of authors protested (S. West¹ and others), some few agreed with Barrs, others were in favor of a middle way: A. Money² would allow white meat but no bread or vegetables; W. Ewart³ advised, besides milk, the early administration of malt, yolk of egg, honey, calves-foot jelly, and similar substances.

Barrs' report, that his cases were not injured by solid food, is, nevertheless, remarkable,⁴ but his advice, to give solid food in every case of enteric fever, certainly goes too far. We assume from his observations, that the experience of giving enteric fever patients scraped meat, softened wheat bread, soft boiled egg, spinach, rice, potato soup, and similar substances need not be harmful, but they should not be recommended as a routine diet for typhoid fever patients. As a rule, up to the time of convalescence, only fluid nourishment should be administered. "But as an appetizer or to ward off threatening inanition, the administration of one or another of the food-substances may be advised occasionally" (v. Leyden).

It remains, finally, to discuss alcohol, which is indicated for other reasons also (to stimulate cardiac activity, see page 57), but, on account of its high combustion value, is not immaterial as food. An enteric patient who is in the habit of using alcohol should have it plentifully from the onset, others only require it in slowly increasing doses during the course of the disease. At the acme of the affection, at the end of the third or during the fourth week, large doses are necessary, a bottle of wine, or even more. Red wine is preferred, in the beginning a light table wine, later a heavy Bordeaux, etc. Also brandy, sherry and other concentrated alcohols are valuable; champagne, warmed wine, etc., are to be kept for special indications (cardiac weakness, etc., see page 57).

C. HYDROTHERAPY AND BATH-TREATMENT

The employment of hydrotherapy in enteric fever is to be referred to James Currie (Liverpool).⁵ In 1787, he advised that the patient be placed into an empty tub and from a height of from 1 to 3 feet or more several buckets of water at a temperature of from 40° F. to 50° F. be poured over his

¹ Brit. Med. Journ., 1897, p. 260.

² *Idem*, p. 1010.

³ *Idem*, p. 1087.

⁴ A diet which is not harmful need not on that account be useful. G. B. Queirolo (La cura dietetica nella febra tifoide, Milan, 1898) advises rectal alimentation in enteric fever. He carried this out in 36 cases, in which the employment of food in a part of the cases occurred exclusively per rectum for thirty-five days. He also emphasizes that he never saw harm from this method. However, this régime cannot be useful nor even advisable; for, according to our present knowledge regarding the value of nutritive enemata, that but fully a quarter to a third of the amount is absorbed, there can be no doubt that his patients during the entire period were undernourished.

⁵ Quoted by Murchison, The Typhoid Diseases, 1867, p. 241.

head and chest. Currie repeated these affusions once or twice daily, and praised their effective influence upon the temperature, the pulse, and upon the condition of the nervous system.

Currie's splendid results stimulated imitation, and the water-treatment of enteric fever, at the end of the eighteenth and at the beginning of the nineteenth century, was very commonly practiced. E. Horn¹ declared in 1814, that this was the only serviceable method of treating enteric fever; Trousseau in France, Schönlein, Niemeyer, and others, in Germany, used and advised it; from Kussmaul's "*Jugenderinnerungen eines alten Arztes*" (Stuttgart, Bonz & Co., 1899), it may be noted that in the thirties and forties of the last century a simple practitioner in the country also understood the value of the water-treatment—but it did not reach general employment, and about the middle of the last century this treatment fell more and more into disuse.

E. Brand (Stettin) revived "the hydrotherapy of enteric fever."² In several publications, he insisted with the greatest energy upon this treatment, and he succeeded with his convincing and confident enthusiasm in again bringing it into use. Jürgensen and Liebermeister, Ziemssen, Immermann, and others assured themselves of the value of the bath-treatment and became warm adherents and pioneers of the method. Thanks to their active propaganda, this treatment was generally accepted in Germany and soon afterwards in foreign countries. The technique of hydrotherapy in enteric fever has been variously altered since then. The conceptions and indications of the action of a bath have been much changed. The bath treatment itself, however, since the time of Brand, has disappeared no more and forms to-day, all over the world, an integral constituent of the therapy of enteric fever.

Brand's method was no less severe than Currie's. The patient was placed in a bath-tub, the water being at a temperature of from 59° to 68° F.; he was well washed with the water, which stood hand-high in the tub, and at the termination of the bath, once or several times, cold water was poured over the back of the head. The effect of the bath was principally looked for in the decline of temperature, the indications for the bath, therefore, depended exclusively upon the height of the fever. The patient was placed in the bath as soon as his temperature reached 102.2° F. or 103.1° F., or even arose beyond this; the baths were repeated 8, 10 or even 15 times during the day.

The success of Brand's treatment was extraordinary, the mortality from enteric fever, wherever this treatment was introduced, declined in an unmistakable manner, usually to one-half of the former figures and below; the early figures being from 18 to 20 per cent. (Griesinger, Murchison) to 10 to 5 per cent. and less. The Munich Military Hospital, for example, showed in Station I, for an exclusive cold-water treatment, a maximum of 5.1 per cent., in Station II, with an alternating treatment, for the most part the treatment consisting of the administration of drugs, 10.8 to 18.7 per cent. mortality.¹

With a distribution of Brand's method, and with the certainty of the value of the bath, the knowledge gained ground, that the effect of this treatment

¹ Compare *Curschmann*, *Der Unterleibstypus*, 1898, p. 433.

² *Die Hydrotherapie des Typhus*, Stettin, 1861.

³ Quoted after *C. Gerhardt*, *Die Therapie der Infektionskrankheiten*. Bibliothek v. Coler, Berlin, 1902, Bd. x, p. 82.

might also be produced by milder means. The cold half-baths were very severe to the patient, who often became very cold, frequently with chattering of the teeth, and was placed back into bed in a cyanotic condition, besides the frequent repetition of the bath was very hard upon the nurses. Full baths were substituted for the half-bath and the temperature of the water was raised. Especially v. Ziemssen's method, to give the bath luke-warm, and while the patient was in it to gradually cool the water by the addition of cold water, was well received, and accepted almost everywhere.

Here and there cold baths are still given, even ice-water baths are advised—on the other hand, warmer baths, at the temperature of 86° F. and of longer duration, up to twenty-four hours, have been advised (Riess¹)—but in general there is a unanimity of opinion that the luke-warm, gradually-cooled bath is sufficient for all purposes in the hydrotherapy of enteric fever. The objects of the bath naturally are now differently considered from what they were formerly. The bath is not a specific method of treatment—as Brand thought—its only value, yes, not even its principal value, consists in the diminution of temperature. The fever is looked upon to-day as a sign of the infection, the other signs of the same: The influence upon the heart, the respiration, the metabolism, the sensorium, are of like importance. It is true, the *uninterrupted fever* in enteric fever, the continued fever, is a danger, and a uniform, continuing temperature of 102.5° F. to 103½° F. or even higher, such as an excessive rise of temperature to 104° F. and over, is still an indication for the employment of the bath. But just as frequent, and no less important indications for the same, are smallness and weakness of the pulse, superficial respiration, a stuporous condition of the patient, or delirium, etc. The bath should decrease the temperature, but at the same time it should freshen and invigorate, increase the blood-pressure and stimulate cardiac action, deepen respiration, clear the mind, and, with this, assist the intake of nourishment, and produce sleep.

For all these indications, in each individual case, there are special rules regarding the time, duration, and frequency of the bath, respectively of the hydrotherapeutic procedures. A hard and fast rule, as was formerly set up, can no longer be given. In general, the hydrotherapeutic treatment of enteric fever is to be conducted in the following manner.

If the enteric fever patient is in a somnolent condition, an ice-bag is placed upon his head, which is removed from time to time, for a short period, eventually, a second one upon the cardiac region (or alternating with the first). Hydropathic coverings upon the chest and abdomen are valuable from the onset; if bronchial conditions or meteorism are present this is especially indicated. Cool ablutions of the entire body, morning and evening, act refreshingly and are to be omitted in no case, for reasons of cleanliness alone. If the sensorium remains clear, and the fever be but moderate, baths are not necessary. If these symptoms, however, develop and the case shows a medium-severe, or even severe course, the bath-treatment is to be begun at once, therefore, with about a temperature of 103.1° F., but even without this rise in temperature, if there is stupor, insufficient cardiac activity, poor respiration, or if

¹ Deutsche med. Wochenschr., 1899, Nr. 40.

sufficient nourishment is not taken. The first bath is given luke-warm, it serves the purpose of determining how the patient will react to it. The first bath had better be given at a temperature of 86° F. and in the course of ten minutes cooled to 77° F. Its effect upon the temperature, which is to be taken one-half to three-quarters of an hour after the bath, its influence upon the pulse, respiration, and the condition of the cerebral symptoms is to be noted. If the patient reacts well to the bath, the next one may be given at a temperature of 80° F. to 70° F. then reduced from 77° F. to 68° F. Lower temperatures than 70° at the beginning of the bath, and reductions to less than 65° are rarely necessary. A medium remission of about 3° as the effect of the bath, is to be looked upon as a sufficient reaction, if only the other actions of the bath, such as the increase of cardiac action, the awakening from the stupor, etc., are simultaneously attained. However, local applications of cold water are to be more utilized for these symptoms, than the general cooling by the bath. At the conclusion of the bath, for which a certain rule is to be given in regard to its duration and its temperature, which should never be prolonged over from ten to fifteen minutes, if there be marked involvement of the sensorium, one or more brief affusions to the neck and back of the head, with poor respirations, râles in the bases of the lungs, with a poor pulse, affusions to the back and chest with water at about the temperature of the room, or slightly cooler, or even ice-water. These cool affusions have an eminently stimulating effect, they produce deep respiration, increase blood-pressure, and moderate the cerebral phenomena.

Regarding the technique of the baths, there remains to be noted, that the tub is to be placed near the bed, and the patient very carefully placed in and taken out of the bath. So long as the patient sits in the water it is to be kept in motion by movements of the hand; the patient is to be washed about the shoulders and neck, eventually carefully rubbed upon the extremities, and is not to be allowed to become cold. It is of service to administer alcohol, or eventually a hot drink, after the bath. At the conclusion of the bath it is best to place him in a second bed, wrapped in a sheet; he is to be quickly and carefully dried, clothed with a shirt, and covered with a warm blanket and allowed to rest. Weakened patients, especially toward the end of the disease, may remain in the damp sheet, without further drying, naturally they are to be warmly covered and allowed to rest for some time. After a period of from one-half to three-quarters of an hour of rest, the temperature is taken and if the patient has reacted well, and shows less temperature, and a clearer mind, this period is to be utilized in giving him sufficient nourishment. Regarding the question of the repetition of the bath, there is no hard and fast rule; it is not necessary, as is so frequently advised, to repeat the bath immediately upon the rise of the temperature to 103.1° F. Eight and more baths per day, as were formerly given in following this rule, mean a decided exertion on the part of the patient, and do not give him sufficient time to gain the necessary rest. If the indications for the bath are taken, not so much from the temperature, as from the other mentioned phenomena, 3 to 4 baths in twenty-four hours, in the greatest majority of cases, will be found to be sufficient.

A bath late at night, around eleven or twelve o'clock, is frequently very serviceable, as at this time the fever commonly reaches its acme, and then

again, because the bath at this time increases the rest of the patient during the night. Liebermeister, in the last few years, as a rule, did not bathe his typhoids during the day at all (only for excessive rise of temperature); the baths were principally given around six o'clock in the evening, 103.1° F. then being the indication for the bath.¹

Contra-indications to the baths not rarely are due to the constitution of the patient: Weak, anemic, fatty individuals, and those suffering from arteriosclerosis, or on account of their tendency to cardiac asthenia, are to be bathed but little and only then with the greatest caution; cold baths and affusions are not well borne by them. Luke-warm baths may be useful, but the pack or washings of portions of the body, which also lead to the same results, are to be preferred. This is also true to an increased extent of older individuals. Patients over fifty years of age are not to be bathed at all, and in those between the ages of forty and fifty, great caution is to be used. Children in general do not react well to cold baths; the usually mild course of the affection in them renders the treatment by baths unnecessary.

The *stage of the disease* also requires consideration: In general, toward the end of the third week, with a beginning of distinct remissions in the so-called stage of abrupt curves, the baths are to be discontinued. The anatomical condition of the bowel (the recent crust-formation in the ulcers), as well as the weakness of the patient, would make it appear that at this time the moving of the patient, which cannot be prevented in bathing, is dangerous. For the same reasons, baths are not used in relapses. Antipyretic measures which are necessary in such instances had better be carried out by milder hydrotherapeutic measures or drugs (see below).

Intestinal hemorrhages and irritative peritoneal phenomena are *absolute contra-indications* to the bath. Regarding the special indications of the hydrotherapeutic treatment for these conditions, and for the individual complications, these will be described later on.

Hydrotherapy employed according to these principles, especially the bath treatment of enteric fever, must be looked upon even to-day as the best method, and strongly advised: It is to be used wherever possible, it makes the course of the affection milder and improves the prognosis. But its special utility has been modified as compared to what was formerly believed: To-day we treat the general condition more than the fever; we prevent and improve complications on the part of the lungs, heart, etc.—with one word, we look upon the hydrotherapy of enteric fever to-day as an integral constituent of the nursing and hygiene of the sick.

D. DRUG-ANTIPYRETIC TREATMENT

Treatment.—A drug-treatment of enteric fever is not necessary in the majority of cases. If, for special circumstances, an indifferent medicine becomes necessary, a mild acid-solution (hydrochloric acid, phosphoric acid, or citric acid), or a gum mixture, or similar substances may be prescribed. Especial drug action, such as the injection of morphia on account of unrest

¹ Doerenberger, p. 4.

or insomnia, the administration of caffein, digitalis or other drugs in asthenia, are indicated by special symptoms; we shall recur to these later on. Here we intend to discuss only antifebrile indications. In the conception of fever and its treatment, a certain change has taken place in the last decade. The view which is held by some authors, that the fever is a curative factor, being a natural reaction against the infection, must for the present still be designated as a hypothesis; and the assumption that the fever dare not be combated as it is necessary to suppress the infection, certainly goes too far—nevertheless, the decrease of the fever-temperature, which may be attained by antifebrile medication, is no longer, as formerly, the chief object of treatment. We previously emphasized that it is most important to combat simultaneously with the fever, the other phenomena of the infection, and we learn to recognize in the cold-water treatment the remedy that is most suitable for this purpose.

The systematic carrying-out of this therapy often gives rise to great difficulties, primarily from the condition of the patient himself—the contra-indications to the bath, which we enumerated above, are not a few—then also, and more frequent, are the external circumstances. The conditions of practice occasionally are responsible for the fact that the use of baths is very frequently impossible or cannot be attained in the required measure. The employment of drugs to combat the fever, therefore, has not lost its importance in general practice in the treatment of enteric fever.

All antifebrile drugs have been given in typhoid, many (for example, kairin, thallin) have been discontinued on account of being harmful; phenacetin (0.25 to 0.5),¹ lactophenin (0.25), antipyrin (0.5 to 1.0), and quinin are still much employed to-day. Especially quinin, that formerly played such a great rôle (Binz),² has lately again been warmly recommended by Erb.³ This author administers at night (some time between seven and eight o'clock) in two doses quickly given one after the other, 1 to 1½, very rarely up to 2 grams of hydrochlorate of quinin and has noticed a marked increase, not only in the following morning remission, but also in the general curve of the next day, including the evening exacerbation, and even after the second following morning temperature; then only upon the evening of this second day is another administration of quinin necessary. Erb believes the second half of the second week of the disease (therefore about the eleventh or twelfth day) and during the third week to be the most favorable times to begin the quinin medication; if this treatment is well borne, it is continued up to the time of complete defervescence: it acts—according to Erb—if not in all, in very many cases decidedly favorably, not only having a purely antifebrile action, but it is “directly favorable upon the course of the disease and abortive regarding the duration of the disease.”

Kernig,⁴ after a continued study, has recently expressed himself very favorably regarding the use of quinin. Goldscheider⁵ also recognizes that

¹ Compare *Doerenberger's* Dissertation, p. 9.

² *Therapie d. Gegenwart*, 1901, p. 49.

³ *Idem*, p. 1.

⁴ *Internat. Beiträge zur inneren Medicin* (Leyden-Festschrift), Hirschwald, 1902, Bd. ii, p. 231.

⁵ *Therap. d. Gegenwart*, 1901, p. 293.

“by means of individually suitable doses of quinin given at the right time, the enteric fever patient may receive some benefit,” but, however, emphasizes, contrary to Erb—*that the water-treatment by no means becomes superfluous by this remedy; this and the nutrition and careful nursing are far more important than the quinin treatment.* An accumulative and schematic treatment by quinin is by no means advisable. In cases in which, for some reason or other, baths cannot be utilized, or in cases where they do not act sufficiently on the temperature, an occasional evening dose, of about 1 gram of quinin may be of value. But only then is quinin to be employed; if it is possible to bathe and the action of the bath is sufficiently favorable, it is, to say the least, superfluous, under some circumstances even dangerous, to administer it.

What has been said of quinin is true in the same sense of phenacetin, lactophenin, and antipyrin, which are preferred by many to quinin, because they lack its disagreeable secondary effects. In cases in which, for one reason or another, the bath treatment could not be fully employed, for example, toward the end of the disease and in relapses, we have very often administered antipyrin for many days, in doses of $\frac{1}{2}$ to 1 gram twice daily, and have noted decidedly beneficial results.

E. TREATMENT OF COMPLICATIONS

Therapeutic interference is often indicated by the not infrequent excessive increase of individual symptoms and the appearance of complications. The most frequent occurrences of this kind and their treatment, especially their prevention, are now to be briefly described.

Digestive Tract.—The importance of the care of the mouth has already been emphasized. False teeth must be removed during the entire course of the disease. Stomatitis must be recognized early before it gains wider distribution; it may be mechanically removed by gentle friction and painting with a solution of borax and glycerin. Parotitis, which rarely occurs if the mouth is well taken care of, is treated by the application of ice; if suppuration occurs, this is favored by cataplasms, and as soon as fluctuation is present, is treated with a proper incision. For vomiting, small pieces of ice are given; an effervescing mixture, and eventually some morphia, may also be administered. During the time in which vomiting continues, the amount of nourishment must be limited; eventually, fluid nourishment, especially milk, must be discontinued entirely and pappy food substituted.

Constipation, which is not so rare (in at least 5 per cent. of all cases), is treated by injection of water or enemata of oil; purgatives are to be strictly avoided, only in the first week of the disease should calomel be administered (see above). More frequently *diarrhea* must be combated. There should not be over 3 to 4 movements in twenty-four hours. The treatment of this condition is to be first attempted by diet. The amount of milk is decreased or diluted, or lime-water is added, starchy soups are given in larger amounts, and are made somewhat more compact; if necessary, pappy food is given (see above). Cocoa, bilberry wine, red wine containing cinnamon and cloves, are often of advantage. Hydrotherapeutic measures are next in importance in

combating the diarrhea. The bath treatment, if it has been instituted early, and systematically carried out, is especially active in limiting the number of stools. Enveloping the belly in moist, warm coverings, between the baths and during the night, acts in the same manner. Only after these measures have proven futile, are drugs in place. Tannin preparations, but especially opium (3 times daily, about 5 drops of tincture of opium or 0.01 extract of opium with 0.25 tannigen of tannalbin) are to be preferred; the combination of quinin and tannin (tannate of quinin) three doses, 0.25–0.5–1, is valuable. Caution should always be observed in employing remedies that constipate; constipation is more serious than moderate diarrhea. If in the next twenty-four hours after employing medication of this kind, no fecal movement occurs, the treatment should be stopped.

Meteorism is also to be combated by dietetic measures—with the same modification of the diet as in diarrhea—and by hydropathic treatment (Priessnitz poultices or an ice-bag upon the abdomen). Formerly turpentine compresses and internal administration of turpentine were advised for meteorism. Very cautious friction of the abdomen with menthol spirit, and alcohol compresses are even employed to-day. More effective are injections of water into the rectum (eventually of cold, even of ice-water), these frequently bringing about marked relief; to introduce the rectal tube very high up into the bowel is not necessary, under some circumstances even dangerous. A trial with the so-called intestinal antiseptics (chlorine water, naphthalin, dermatol, or others), which are said to diminish decomposition and formation of gas in the intestine, may be made. But the restriction of food, eventually the exclusive nourishment with carbohydrates (flour soup, ultimately grits, rice, and similar substances) in combination with hydriatic measures, are of much greater importance and are almost always successful.

Each movement must be investigated so that an *intestinal hemorrhage* will be noted at once. If this occurs, complete rest of the patient is necessary: The baths are stopped (usually permanently), at least, however, from ten to fourteen days, food is limited to the minutest amounts, in the first few days the patient has only a tablespoonful of cold drink, some ice-cold milk (also by the tablespoonful) and pieces of ice. An ice-bag or a frozen compress is placed upon the abdomen. Naunyn advises increasing the action of the cold by ice-water injections into the rectum; if the ulcers be deeply seated these injections also serve a cleansing purpose for the bleeding surface. He advises that the water be allowed to flow through a large funnel (without especial pressure) and by lowering this, allowing the water to immediately flow out again; the washing is continued with large quantities of water until it is no longer hemorrhagic upon flowing out. I frequently used this treatment in Naunyn's clinic and have seen good results. The bowel, in each case of hemorrhage, is quieted by large doses of opium (up to 5 times 0.03 extract of opium and more), this being continued in decreasing amounts for several days after the hemorrhage has ceased. Internal hemostatics are very questionable in their action, but iron-chlorid or hydrastis is usually given. In continued hemorrhage, a trial with the gelatin treatment is to be advised (100 cc. of a 1 to 2 per cent. gelatin solution, subcutaneously or by enemata). In a serious anemia, a salt infusion is indicated. Nourishment should be instituted very

gradually and cautiously, up to its former amounts and constituents, only after a number of days have passed (five or more) after the hemorrhage has ceased.

Peritoneal irritation also requires absolute rest, cessation of the baths, limitation of the food, ice compresses to the abdomen, and opium. If a *perforative peritonitis* has occurred, only an immediate operation gives hope of recovery.

Respiratory Tract.—*Epistaxis* at the onset of the affection is usually of slight importance and is generally easily stopped by cold (ice) compresses. If the condition be very severe and tampons become necessary, this treatment must be simultaneously carried out both anteriorly and posteriorly. With a simple anterior tampon, the blood easily flows off posteriorly, and cannot be noticed on account of the stupor of the patient, and thus gives rise to dangers. In the later stages of the disease, epistaxis, besides other hemorrhages, from the gums, etc., may be the signs of a scorbutic diathesis. In such a case the diet must contain vegetable nourishment (spinach, mashed carrots, apple sauce, fresh fruit-juice, etc.).

The *milder affections of the pharynx and larynx*, which are often prevented by careful nursing of the patient, do not usually require local treatment. However, if the disease invades the deeper structures (abscess, *perichondritis*), a timely and energetic interlaryngeal treatment becomes necessary; to prevent immediate danger, tracheotomy will often be indicated. The *dysphagia* due to these complications must be combated by nourishment through the stomach tube.

Of greater importance are the *affections of the bronchi and lungs*, to which enteric fever shows a special inclination. A mild bronchitis is present in most severe cases of typhoid fever, and bronchopneumonia is very frequent, due to hypostasis and the faulty swallowing of the soporous patient. Its prevention, which is easier than its treatment, must be thought of from the beginning of each case. Priessnitz compresses to the thorax, affusions to the back in connection with baths, sitting up and alteration of the position of the patient, and, further, care in feeding (the patient should always be slightly raised when fed) are the best measures of prophylaxis. The same remedies carried out with greater energy (frequent, very cool affusions to the back, ice-bags) must be employed if hypostatic or deglutition pneumonia is already present.

Besides this, especially plentiful amounts of strong alcoholic drinks are of value.

Expectorants are of much less importance. *Liquor ammonii acetatis* is preferred but apomorphin, ipecac, or senega may be given in small doses; however, their value is questionable.

Pleurisy, which usually occurs in connection with other pulmonary affections, is treated upon general principles; it forms a contra-indication to baths.

Circulatory Apparatus.—The special danger of the stage of decline and of convalescence in enteric fever is due to *cardiac asthenia*. To prevent this, is the especial object of nutrition and bath treatment.

Increasing weakness of the pulse, we have seen to be an important indication for the bath, as increase in blood-pressure is an unquestionable result of this treatment. The diminution in the cardiac action is further to be com-

bated by alcohol; at first it should be administered in small amounts, but increased from week to week. At the end of the third or in the fourth week of the disease, in the case of an adult typhoid patient who in the time of health is used to a certain amount of alcohol, there may without danger be administered to him one bottle or even one bottle and a half of strong wine, daily. After the fever has ceased, these large doses may soon be diminished.

In acute attacks of weakness (collapse) champagne, warm wine, old brandy, hot, strong coffee are necessary. Among drugs, small doses of digitalis or strophanthus if necessary may be given for a longer period; injections of camphor, caffeine, also strychnia are to be reserved for immediate danger.

Nervous System.—For the *somnolence* upon the one hand, and for the *conditions of excitement* on the other, the bath treatment is the most effective remedy. Ice-bag to the head, cold affusions to the head and back, and a luke-warm bath are to be used in the former case, warm, up to luke-warm, baths, for the latter condition. Unrest and delirium, especially *insomnia*, require the use of morphia. We need not be too sparing with this remedy. If in the evening, a luke-warm bath and a cup of valerian tea, with some bromide are not effective, the patient being sleepless, restless, delirious all night, then an injection of 0.005 to 0.01 morphia, which will give him necessary sleep lasting several hours, is the greatest blessing. If this acts well at the height of the disease, it may be continued for one week or even longer, night after night (or omitting a day) without there being danger of morphinism on this account.

Urinary Passages.—In *nephritis*, which is quite rare as a complication of enteric fever, cold baths are to be discontinued, mild hydropathic measures (luke-warm baths and compresses) are permissible. If the patient be markedly soporous, filling of the bladder should be looked after; if necessary, the urine must be drawn off with a catheter. *Cystitis* and *bacteriuria* are treated with urotropin (0.5 grams three times daily), according to Schumburg;¹ this inhibits the development of the bacilli, without, however, destroying them.

It is not necessary to describe the various other complications, for example, the not infrequent post-typhoid suppurations, which require the usual treatment which is indicated for them. Finally, I should like to emphasize one point, which may have been sufficiently noted from the description in this chapter, that also particularly in the complications of enteric fever, drug therapy is far inferior to nursing, to nutrition, and to the bath treatment of the patient. The entire therapy of enteric fever depends especially upon these three conditions.

F. TREATMENT OF CONVALESCENCE

The first afebrile day is not necessarily to be looked upon as the onset of convalescence. In mild cases, even during the time of the remittent stage of the fever, the appetite returns, and with complete apyrexia, the joyful sensation of recovery is soon experienced. But after every severe affection, even in the period of apyrexia, the sensation of weakness is still great and there can be no thought of convalescence for many days; the temperature is subnormal, the

¹ Deutsche med. Wochenschr., 1901, No. 9.

pulse is increased, the secretions of the mouth and stomach are still insufficient, the splenic tumor has not entirely disappeared. Curschmann has called attention to the fact, that in the greater number of cases loss of body-weight still continues during the first, even in the second, very rarely in the third week after complete apyrexia. He has noted after severe, long-continued affections, sometimes, however, after shorter and milder cases, a loss of weight of from $1\frac{1}{2}$ to 2 kilograms in the first week of the period of apyrexia. Convalescence begins only when the subjective sensations of the same appear, when the weight increases, and the strength returns. Until this is the case, the nutrition of the patient is comparatively easily carried out and does not give rise to difficulties; without much trouble he remains upon the same diet as during the last weeks of his fever. But the situation becomes very trying after the appetite returns, especially if it is particularly marked, as is usually the case, the patient anxiously asking for greater amounts and more compact food, for his requests must not be complied with under any circumstances. The intestines still require great rest and care; the administration of compact food too early, or of too large amounts of food during the first period of convalescence are the usual causes of exacerbations and relapses, as experience teaches daily. In general, the change from fluid to solid diet can only be risked after a number of days—the number of days cannot be absolutely determined but, in general, seven to nine days may be sufficient—and this must be instituted cautiously and slowly. The patient, by this limitation of nourishment, only suffers subjectively; objectively, it may be proven that the diet of the febrile period, when the most important consuming factor, the fever, is absent—provided that convalescence has actually begun, and is markedly continuing—is sufficient to maintain and even to increase the body-weight. After a reduction in weight from 129 pounds to 111 pounds, Barth determined in his typhoids, upon the average, in the first week of convalescence by continuing the same diet, an increase of weight to 118 pounds.

Only in the second week, therefore after about seven afebrile days, may a soft boiled egg, some softened zwieback or a cake, a little jelly, mashed potatoes or similar substances, be given in small amounts and with a careful observation of the temperature and the feces. If these are well digested, sweetbreads and brain, scraped meat, oysters, caviar, and toward the end of the second or beginning of the third week, easily digested vegetables may be given, however, in small, eventually frequently-repeated, portions. During this entire period milk and soups are to form the mainstay of the diet. Four weeks, and under some circumstances a longer period, must elapse before the gradual return to normal food should be complete. Heavy foods such as varieties of cabbage, leguminous fruits, raw fruit, etc., are to be abstained from for months.

Now a second question will be put to the physician, which, besides the diet, is the next in importance in convalescence, the question of getting out of bed. This is an important step for every patient who has gone through a severe disease; if permitted too early, or incautiously carried out, it may produce severe, yes, permanent injury. Naturally, a certain day cannot be indicated, it depends upon the progress of convalescence. However, before the patient takes solid food, the bowels must be in order and temperature and pulse normal, usually, therefore, not before the third to the fourth week of convalescence

should he be permitted to get out of bed. Above all, however, the first getting up is to be carried out with caution and in the presence of the physician. The patient must be prepared for this, in that he has already sat up in bed and moved about—which must only take place gradually during the second or third week—and then but for a short time, from one-half to one hour, from the bed to the lounge or to an easy chair without tiring himself by dressing, etc.; he should return to bed before the signs of exhaustion occur, briefly, the entire act must at first be of a more passive character. Only gradually and with assistance, are more active movements to be allowed, while simultaneously the time of being up may be more and more prolonged.

[The general practice in the United States is to allow the patient, when no special contra-indication is present, to sit up in bed more and more each day in the second week after the defervescence is complete and to sit up in a chair for increasing periods in the third week. After that he may go for a short drive or walk.—ED.]

If convalescence is carefully guarded in this manner, a permanent damage of health need not be feared, even after a severe attack. The patient recovers from the long affection, becoming as strong as previously, not rarely is he even in better condition than before.

This, however, takes months. In the most favorable case the occupation cannot be resumed under three months, if the affection has been severe it may be even six months. A rest in the country, or at some resort, in the winter in the south, is to be advised for the last period of convalescence, if these conditions can be attained.

[See also Serum Therapy, page 909.]

PARATYPHOID

BY DR. ALBERT BRION, STRASSBURG

HISTORICAL REVIEW

Paratyphoid Bacillus.—The name paratyphoid was first used by Ch. Achard¹ and R. Bensaude.² In November, 1896, they communicated to the Société Médicale des Hôpitaux of Paris, the observations of two “infections paratyphoïdiques”; in these two cases—the clinical course of which showed great similarity to enteric fever, even to the extent that this diagnosis was permissible, even forced itself—the above-mentioned authors isolated, once from the urine, at another time from a sterno-clavicular suppuration, a bacillus which showed great similarity to the Eberth-Gaffky bacillus, however, differing from it, primarily by its property of fermenting certain carbohydrates and, for this reason, the above-mentioned authors called it “bacillus paratyphoid.”

This name found little favor; in the discussion which this communication caused, Widal proposed for the bacillus the name “paracolon bacillus,” for the cases observed by Achard and Bensaude the name “paracolon bacillus infection,” as he would not recognize its similarity to typhoid and believed the bacillus to be identical with that described by Gilbert and Lyon,¹² the paracolon bacillus.

The importance of the Eberth-Gaffky bacillus to enteric fever has been generally recognized since 1884. We know that since its discovery, up to recent times, the following facts have appeared to be of general value: 1. The bacillus of Eberth is found in every case of enteric fever; 2. A disease in which another bacillus is found is not typhoid fever.

In this manner, it is to be understood that Widal, who combated the name paratyphoid, nevertheless, was the first one who—without knowing it—saw a true, classical case of paratyphoid:

In 1897 Widal and Nobécourt³⁶ described a paracolon bacillus, which they had cultivated from an abscess of the neck in a phthisical patient, and that showed the complete cultural properties of the bacillus described by Achard and Bensaude. When Widal and Nobécourt tested the properties of their bacillus with the serum of various typhoid patients, they found that, in general, their bacillus was uninfluenced; *only the serum of a convalescent from a “classical” typhoid showed agglutinating properties with the paracolon bacillus in the proportion of 1:12,000, whereas the same serum with the Eberth bacillus showed it only in the proportion of 1:20.*

At that time Widal assumed that this paracolon agglutination was the expression of a secondary paracolon infection in true enteric fever, id est, a primary infection with Eberth's bacillus, which was assured by the agglutination of the latter bacillus—at the height of the infection amounting to from 1:100. According to the experiences of the last few years regarding paratyphoid, we must unquestionably look upon this observation as the first certain case of paratyphoid and, later on, we shall prove this somewhat more conclusively.

In the following years a number of cases were published in Baltimore and New York, by Gwyn,¹⁴ Brill,⁵ and Cushing,¹⁰ which could not be differentiated in general from the clinical picture of enteric fever; however, the blood serum of the cases did not agglutinate the Eberth bacillus, whereas the "paracolon bacilli," cultivated from the blood by puncture of the spleen from secondary suppuration, showed a strong specific agglutination.

It was Schottmüller^{31 32} who was the first in Germany to call attention to the great special importance of the absence of Eberth bacilli and of the presence of similar bacteria in cases of enteric fever, and who instituted systematic investigations regarding this point. In Hamburg he observed in the course of a typhoid epidemic, seven cases which showed the classical symptoms of enteric fever; however, in the blood, in six cases, instead of the Eberth bacillus for which he looked, he found other typhoid-like rods which showed the properties of the above-described "paracolon bacillus"; the serum of all seven cases retained the same agglutinating properties as that of the "paracolon infections."

How were these seven cases to be grouped? Clinically they resembled enteric fever sufficiently to be mistaken for it, therefore, a name must be chosen for the bacillus, which would call attention to this clinical likeness, and so Schottmüller logically designated these seven cases as paratyphoid, and the bacillus that was found, as the paratyphoid bacillus—although in culture and, as we shall see, also in regard to its property of agglutination, it did not differ at all from the paracolon bacilli of Widal, Cushing and others.

Almost simultaneously, but independently of Schottmüller, a publication of Kurth²² appeared. He had observed in Bremen five more or less severe cases of enteric fever, the serum of which did not agglutinate the Eberth bacillus. In two cases he isolated, from the urine, then from the feces, his "bacillus bremensis febris gastricae," that agglutinated the serum of his patients in proportion of 1:250 to 1:8,000.

Bruns and Kayser⁷ have shown by agglutination and comparative cultures that this bacillus of Kurth is identical with those described by Schottmüller (Seemann).

In Strassburg, Kayser and Brion⁶ isolated from the blood, from the eruption, from the urine, the feces, the vaginal and urethral mucous membrane of a patient, who showed typhoid symptoms, a bacillus which, by agglutination, they identified with the other bacilli of the Schottmüller type.

To compare the different paratyphoid observations with each other and, in order to classify them, Kayser recognized two types, namely, bacillus paratyphoid A, and bacillus paratyphoid B, which differed by slighter cultural properties and especially by their sensitiveness to agglutination. The Strass-

burg cases belonged to type A, the Bremen cases to type B; of the seven Hamburg observations, three belonged to type A and four to type B.

In the last few years nine cases were described in Baltimore, New York, Philadelphia and Liverpool by Colemann and Buxton,⁹ Johnston,²¹ Hewlett,¹⁷ Longcope,²⁶ Libmann²⁵ and Hume,¹⁴ all of the cases showing typhoid symptoms, but neither a "paracolon" bacillus nor a "paratyphoid" bacillus could be isolated, which resembled the bacillus of Gwyn, Cushing and Schottmüller; according to the results of these investigations, the microorganisms in the seven cases belonged to type A, and in two cases (Longcope¹ and Libmann) to type B.

In connection with these more or less sporadic cases, three paratyphoid epidemics are to be mentioned.

In Eibergen (Holland) de Feifer¹¹ observed fourteen cases, from the blood serum of which Kayser (Strassburg) made a diagnosis of paratyphoid, that of type B; the agglutination power of the serum varied from 300 to 5,700.

Hünemann²⁰ reports from Saarbrücken (Rhine Province) nineteen cases which he observed during a typhoid epidemic, in which he cultivated from the feces or the urine a bacillus resembling typhoid, which agglutinated with the blood serum of the respective patients in the proportion of 1 to 200.

A third epidemic was described by Sion and Negel in Jassy (Roumania): Five inhabitants of a house were affected with typhoid symptoms; in the blood of four patients, an "atypical coli bacillus" was cultivated. The immune serum of an animal treated with this bacillus agglutinated the immunized bacillus 1 to 4,000, the typhoid bacillus and coli bacillus only 1 to 500, therefore, this atypical coli bacillus is neither the typhoid bacillus nor the bacillus coli, and as its cultural properties coincide with our paratyphoid bacillus we may place it in this category, and also the described epidemic, although it was not designated by the authors as paratyphoid but as pseudo-typhoid. In the epidemic of Saarbrücken, as well as in that in Jassy, accurate and comparative bacteriologic investigations were not recorded, so that we are unable to determine in which of the two paratyphoid groups we are to place them.

THE PARATYPHOID BACILLUS

The importance and distribution of paratyphoid will be seen from this historical review: Since 1896, sixty-six cases of this kind have been described in Paris, Baltimore, New York, Hamburg, Bremen, Strassburg, Philadelphia, Liverpool, Eibergen, Saarbrücken, and Jassy. As the majority of these cases have been described in the last few years and in constantly shorter intervals and in increasing numbers, it is to be expected that observations regarding paratyphoid will greatly increase in the near future.

Summarizing our present investigations, I shall attempt to describe the position at this time—the end of 1902—of paratyphoid in a bacteriologic, symptomatologic, diagnostic, anatomic and general pathologic respect.

The bacteriology of paratyphoid has been minutely investigated by Cushing,¹⁰ Schottmüller,³² and Kayser.^{6 11}

In the following I shall give the results of the investigations of Kayser:

The bacterium (negative according to Gram) is actively motile, in shape and size resembling the bacterium coli. The rods in the animal tissue (blood, spleen) show an intense polar stain after a brief carbolfuchsin staining. The *gelatin colony* has a lardaceous lustre, is pale gray, transparent and iridescent. In contrast to colonies of bacterium coli, the vein-like surface indentation is absent. The shining, round colony, only rarely showing indentations, may without difficulty be differentiated from the bacterium coli; a picture different from that of the bacterium coli can also be seen in the gelatin stroke culture; the growth in breadth is less intense, and the large marginal growths are absent. In neutral red agar, in thirty-six hours, a distinct greenish fluorescence appears; the agar column clears more slowly than in the case of the bacterium coli, bouillon becomes uniformly cloudy, not so intense, however, as by the bacterium coli. Even after weeks, indol cannot be recognized. Milk is not altered. In litmus whey there is the same behavior as in the case of the typhoid bacillus.

Regarding the different varieties of sugar, dextrose and maltose are strongly fermented. In lactose bouillon—provided it does not contain muscle sugar—type A forms a visible air-bubble, whereas type B shows decided fermentation, about four times less strong than the bacterium coli.*

The pathogenicity is marked in white mice and in young guinea pigs; the animals die, showing the picture of sepsis. However, pyogenic properties could also be observed in the animal experiment.

Bacillus paratyphoid B differs from type A by its thicker, whiter gelatin colonies; type B, only from the second week on, alkalizes sour whey and clears milk completely. Its behavior to lactose bouillon has been described above.

DIFFERENTIATION FROM ENTERIC FEVER

According to the general opinion of authors, paratyphoid cannot be differentiated from enteric fever by its symptoms; there is no single symptom that is observed in paratyphoid that does not belong to the clinical picture of enteric fever.

Johnston,²¹ de Feifer and Kayser,¹¹ from a very careful compilation, have calculated the percental appearance of each symptom in the previous paratyphoid cases; the cases published since that time are but little changed regarding this data. We note that paratyphoid is a slowly-developing febrile disease, beginning with headache and disturbance of the general health, lasting from three to four weeks, in 80 per cent. of the cases showing an eruption and enlargement of the spleen, in 30 per cent. of the cases a diazo-reaction of the urine, in 18 per cent. "pea-soup-like stools," 5 per cent. of the cases showing intestinal hemorrhage, herpes labialis occurring in 3 per cent. The other symptoms, as in the case of enteric fever, vary to an extraordinary degree; there are transitional forms, from cases of the severest kind with delirium and a severe damage to the general condition, up to the mildest, which present

* These results, which differ from those previously given, are from new investigations of bouillon free from muscle sugar (*Kayser, Brion*), and correspond also with the observations of other authors (*Cushing* and others).

themselves as a simple gastric catarrh, even without fever (*paratyphoid ambulatorius*, de Feifer and Kayser).

Among the complications, bronchitis is very frequent, paresis of the deltoid has been noted once (Achard¹), twice an osteo-chondral suppuration (Achard,¹ Cushing¹⁹). Relapses are very rare.

The height and type of the fever are the same as in typhoid. Only in some few cases, toward the end of the fever period, decided remissions in temperature have been observed (Kurth,²² Brion and Kayser,⁶ Colemann and Buxton⁹).

The mortality is a conspicuously small one; up to the time of this writing, but two positive deaths have occurred; the case of Longcope and that of Sion and Negel, therefore giving a mortality of 3 per cent.

In the literature I find two more fatal cases due to paratyphoid, one reported by Libmann²⁵ and one by Strong.³⁴ But I do not find these cases to be free from objections. In the case of Libmann, a mixed infection of typhoid and paratyphoid must be thought of, on account of the peculiarities of the serum reaction; that such a mixed infection is possible has been proven by de Feifer and Kayser,¹¹ by separate agglutination tests. The patient of Libmann was operated upon on account of a probable purulent cholecystitis; from the bile, a bacillus paracolon was cultivated, which agglutinated the blood serum of the patient in the proportion of 1 to 100; however, it also agglutinated the Eberth bacillus in the proportion of 1 to 200, later on, the reaction disappeared to the paracolon bacillus, whereas the reaction of the Eberth bacillus still existed.

At the autopsy, typhoid ulcers in the stage of healing were found in the ileum.

The case reported by Strong³⁴ is even more conspicuous: From the cadaver "which was already markedly decomposed," the remains of a soldier who had perished from an affection, with high fever in forty-two hours, in July (!), from the spleen after death, a "paracolon bacillus" was cultivated. No agglutination tests were attempted with the serum of the corpse nor with other bacilli. As the author expresses the probability that his bacillus may have been a "post mortem invader," we can only agree with this suspicion.

PATHOLOGY

As up to this time there are but two fatal cases of paratyphoid, that of Longcope²⁶ and that of Sion and Negel,³³ the material from which the pathological anatomy must be described is a very meagre one.

From the autopsy report of Longcope, we note that the spleen of his twenty-two-year-old patient was decidedly enlarged: It weighed 460 Grm., the liver weighing 1,810 Grm., and the heart 345 Grm.; the spleen was extraordinarily soft, the capsule soft, tender, grayish-red; the pulp was soft and friable. Liver and kidneys showed on their cut-surfaces, the evidences of cloudy swelling. A few microscopic focal necroses could be found in the parenchyma of the liver. Regarding the intestine, the solitary follicles in the colon were visible as small grayish points, having a diameter of 1 mm. In the small intestine, no swelling was present, neither in the solitary follicles nor in Peyer's patches, and, outside of a few emphysematous mucous-membrane

areas, the ileum, jejunum, and duodenum showed nothing abnormal. Besides these findings, there were large amounts of ascarides.

The autopsy report of the Sion-Negel case was that of sepsis: Enlargement of the spleen, endocarditis, cerebral emboli, renal infarcts. In the intestine and in the mesenteric glands, no signs of enlargement were present.

In a certain sense, complementing the sparsity of the anatomical material at our disposal in paratyphoid, is the appearance of intestinal hemorrhages during the course of the disease (Achard, Hume, Gwyn, de Feifer and Kayser). This would make it likely—although intestinal hemorrhages occur in pure sepsis—that, in spite of the absence of the intestinal ulcers in the cases of Longcope and Sion-Negel, they, nevertheless, occur in paratyphoid, and that, therefore, between the anatomical findings of paratyphoid and those of enteric fever there would be just as little difference as in the clinical picture.

The scarcity of typical intestinal lesions, finally, need not appear so very strange: We know that the typical symptom-complex may be present without observing the classical findings of Louis in the cadaver. We must remember, primarily, that in enteric fever of children, in a compilation of Henoch,¹⁶ only in 16 per cent. of the cases typical typhoid ulcers occur, and in 46 per cent. the ulcers are entirely absent! Further, it must be recollected that a number of enteric fever cases without intestinal lesions have been described, such as the cases of Chiari,⁸ Opie,²⁹ Blumenthal,³ and others. Whether, on the other hand, in these earlier cases of "typhoid septicemia," paratyphoid cases are included, cannot be decided, for the reason that agglutination comparisons formerly were not quantitatively determined, and because we find values of 1 to 10 up to 1 to 50 for typhoid bacilli, in the numbers which have been determined as agglutination values, values which in the blood serum of paratyphoid infection may easily be attained by the group agglutination which is soon to be described.

DIAGNOSIS

We now come to the discussion of the *diagnosis* of paratyphoid. This cannot be made from the symptoms at present: *Up to this time there is no symptom by which enteric fever can be differentiated from paratyphoid.*

The *suspicion of paratyphoid* is aroused by the absence or the conspicuous feebleness of the Widal reaction of typhoid bacilli; if then the serum agglutinates a legitimate paratyphoid bacillus in 1 to 100 or much more markedly than the Eberth bacillus (for example, in the Widal case: Eberth 1 to 20, paratyphoid 1 to 12,000), the diagnosis of paratyphoid is to be made if the clinical picture of enteric fever is present. Naturally, the case is also decided if from the blood, or from the secretions or excretions of the body, a bacillus may be cultivated which agglutinates the serum of the patient to a high degree (at least 1 to 50!), and that the immune serum of an animal previously treated with a true paratyphoid bacillus shows the same high agglutinating properties as the immunizing bacillus.

In this manner, the cases which have occurred up to now may be separated into two groups according as their serum agglutinates, paratyphoid bacillus A or B.

By the kindness of Dr. Widal and Dr. Achard I have been able to examine the bacillus paracolon Widal-Nobécourt, as well as the bacillus paratyphoid of Achard-Bensaude. It has developed that a paratyphoid immune serum that has a macroscopic agglutination maximum of 1 to 2,000 for the bacillus paratyphoid B agglutinates the bacillus Widal-Nobécourt ad maximum macroscopically 1 to 2,000, the bacillus Achard-Bensaude B also in 1 to 2,000, the bacillus Achard-Bensaude W 1 to 1,500.

Therefore, according to our present postulates, it is justifiable in identifying bacteria, to place the bacilli of Achard and of Widal into the category, paratyphoid B.

We must, however, reflect, that between the bacillus paratyphoid B and the bacillus of enteric fever, a *group agglutination* exists (Pfaundler,³⁰ Bruns and Kayser⁷), i. e., a high value B-serum may agglutinate typhoid bacilli, and vice versa. In this manner, Widal's case³⁶ is to be explained: The serum of a convalescent from a "classical typhoid" agglutinates the paracolon bacillus in 1 to 12,000; it was, therefore, of high valuation, and with a pseudo-Widal test a reaction up to 1 to 20 was observed, i. e., as the result of the existing group-relationship between the Eberth bacillus and the bacillus paratyphoid B, agglutination occurred, even though to a much feebler extent.

However, it is not sufficient to make a diagnosis of paratyphoid from the bacteriological proof of the bacillus nor from the serum reaction alone; *above all, the symptoms of enteric fever belong to the clinical picture of paratyphoid.* We must, therefore, exclude that case of Widal's in which he cultivated his "paracolon bacillus"—although by most of the previous authors it has been counted as a case of paratyphoid: A tubercular patient suffering from an abscess of the neck developed a temperature for three days, but never showed a symptom suspicious of enteric fever; it was not a case of "paratyphoid" although his serum agglutinated the bacillus paratyphoid B in 1 to 1,000, although this serum reaction upon further investigation diminished, although in the abscess of the neck—in place of the usual pyogenic organism—a paratyphoid bacillus was found! Nor do we speak of enteric fever, if typhoid bacilli are cultivated from pus, in a patient who is otherwise healthy, who formerly may have suffered from an attack of enteric fever.

If we argue in this sense, the case described by Kayser and Brion⁶ is not a positive case of paratyphoid as the possibility of a primary infectious vaginal disease, and a general infection with paratyphoid bacilli originating from this, thereby producing a modification of the clinical picture, in which there were already sufficient typhoid symptoms present (spleen, eruption, etc.), must be admitted.

PATHOGENESIS

Regarding the proper appreciation of the *pathogenic importance* of the paratyphoid bacillus, the previously described finding of Widal is very noteworthy, for it follows from this that the human organism may contain the paratyphoid bacillus without giving rise to typhoid symptoms. It is possible that this must be dependent upon the mode of infection. Other explanations, however, cannot be put aside: In Widal's case the patient, twenty-three years

previously, probably had an attack of enteric fever; shall we assume that this affection was paratyphoid and that, as the result of this, virulent bacteria had still remained? Or is the distribution of paratyphoid bacilli in nature as great as that of the pyogenic organisms?

Regarding the occurrence of paratyphoid bacilli outside of the organism—with the exception of the finding of bacilli in the water-supply in their house epidemic in Jassy, by Sion and Negel—up to the present, nothing is known. The paracolon bacteria are more frequently looked for and found than the paratyphoid bacteria, which do not differ in culture from the paracoli only in regard to their agglutination properties. In this category also belong the psittacosis bacteria.^{23 27 28} The latter play an especial rôle in the paratyphoid question, as the two first paratyphoid observations were later explained by their authors, Achard and Bensaude, as psittacosis infections.

By comparative agglutination, I have, however, determined that neither the bacillus psittacosis, origin Gilbert-Fournier,¹³ nor those originating from Nocard,*²⁸ nor those originating from Pasteur Institute † are agglutinated by paratyphoid immune B-serum in a macroscopic test if 1 to 2,000, the same serum, however, agglutinating both paratyphoid bacilli of Achard in 1 to 2,000 and 1 to 1,500.

Further, there belong in this group the *toxic meat bacteria*; the principal ones have been examined by Kayser⁶ regarding their sensitiveness to agglutination and have been found to be uninfluenced by paratyphoid immune serum.

ETIOLOGY

Regarding the mode by which the paratyphoid bacilli reach the patient, nothing can be learned from the sporadic paratyphoid cases regarding the origin of the disease. It is different, however, in the epidemics of Eibergen and Jassy. We agree with a view of de Feifer and Kayser, Sion and Negel; on account of the manner of distribution and on account of the proof of the bacilli in the water of the infected houses, namely, that these epidemics are of aquatic origin.

Still another mode of infection must be mentioned: I mean infection by eating meat. Levy and Jacobsthal²⁴ have determined legitimate typhoid bacteria in beef; and, on the other hand, we know that in the recognized cases of meat-poisoning, bacteria have been demonstrated which in culture are much nearer the paratyphoid bacilli than they are to the typhoid bacilli.

Suter³⁵ has tabulated the old epidemics of meat-poisoning occurring in Andelfingen, Kloten, Birmensdorf, and Würenlos. The clinical course as well as the anatomical findings and the medullary swellings of Peyer's patches, typical typhoid ulcers of the ileum, even perforative peritonitis, determined, at least in the three last epidemics, the diagnosis of enteric fever. Bollinger,⁴ however, believed that they were not cases of actual "human enteric fever," but that a "variety" was present and, among other reasons, on account of the conspicuously slight mortality of the meat-poisoning, namely 1 to 2 per cent.

* Kindly placed at my disposal by H. Achard.

† From the laboratory of Král in Prague.

We remember that paratyphoid up till now shows a mortality of 3 per cent. Far be it from me to deduce the identity of the two diseases from the slight mortality—there are even very mild typhoid epidemics. It is sufficient to call attention to the conspicuous similarity between affections caused by meat-poisoning and paratyphoid and to the possibility of infection by the eating of meat.

EPIDEMICS

Before we consider which bacteria are found in the symptom-complex “enteric fever” in connection with the previous explanation, I must still briefly relate an epidemic of “colibacillosis pseudotypica” in Weltevreden near Batavia: de Haan and Kiewit de Jonge¹⁵ observed twenty-three soldiers who, shortly after a military campaign were gradually taken ill with headache, lassitude, vomiting, and a step-like rise in temperature. At the acme of the disease, a roseolar eruption appeared, also splenic tumor, diarrhea, intestinal hemorrhages, stupor and delirium. The convalescence was mild; no relapses occurred; nevertheless, they were dealing with a severe disease, as four of the affected ones died. At the autopsy, in one case, a large ulcer, with undermined borders, besides two smaller ulcers, were found in the ascending colon. There was no enlargement of Peyer’s patches, nor of the solitary follicles. The spleen was enlarged, but there were no other signs of enteric fever. The serum reaction to typhoid bacilli = 0, on the other hand, the serum of eleven of the patients agglutinated a cultivated bacillus taken from the spleen immediately after death, in 1 to 50 and 1 to 160. The authors are, therefore, convinced that the patients in whom the serum was examined suffered from the same infection as did those who succumbed. The bacilli proved themselves to be *bacillus coli communis*, with all of their typical properties (coagulation of milk, indol formation)! It, nevertheless, is remarkable that the agglutination values which these authors obtained with the serum of their patients, upon coli bacteria, were very slight and that they never rose, as is so common in enteric fever and paratyphoid, to proportions of hundreds, yes, even of thousands.

SUMMARY

The most recent bacteriologic investigation of the symptom-complex, which we recognize clinically as enteric fever, has therefore shown that not alone the Eberth bacillus is met with in this affection, but also other bacilli, which stand between typhoid and coli, yes, perhaps coli bacilli themselves (epidemics of de Haan and de Jonge—reserving our consideration just described regarding the coli bacillosis pseudotypica).

If it is, therefore, certain that Eberth’s bacillus—although in a very small percentage of cases (6 per cent. de Feifer and Kayser¹¹) (Hoffmann²⁸)—may be substituted by other bacilli which show cultural differences; we, nevertheless, have not the slightest cause to doubt the specificity of the bacilli and the disease: *Bacillus coli communi*, bacilli paratyphi A and B, *bacillus typhi abdominalis* may still be differentiated sufficiently by their cultural properties

and, although in their laboratory existence this or that cultural character, for example, their growth upon gelatin, may be modified, nevertheless, they remain so well differentiated that a confusion is impossible.

That they are closely related, cannot be gainsaid; that in the course of their development they are derived from a common primitive type is possible; at this time, however, the assumption, that under any circumstance whatsoever a colon bacillus might change to a paratyphoid, or a typhoid bacillus might develop from this, would be a hypothesis without the slightest foundation; on the contrary: In the specific agglutination we see the expression that these diseases—be they typhoid, paratyphoid, or infection by coli bacteria—are throughout specific, i. e., that, regarding their origin, they are either directly or indirectly due to diseases that have the same bacterial findings. Therefore, the Gruber-Widal reaction, in spite of the damage which it has apparently suffered, has retained its full importance.

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TYPHUS FEVER AND RELAPSING FEVER

By L. LICHTHEIM, KÖNIGSBERG

HISTORY AND ETIOLOGY OF TYPHUS FEVER

UNDER the term "typhoid diseases," in the course of the last century, enteric fever, typhus fever, and relapsing fever were included, three diseases that have almost nothing in common except the unfortunate name typhoid. This term was originally given to a symptom-picture which almost always exists in typhus fever, in enteric fever only in the minority of the cases, and in relapsing fever only exceptionally, and besides, is not even limited to the typhoid affections. If it is asked, what has led to the designation of this pathological group as typhoid diseases under these circumstances, it must be answered that it was principally error. Originally the name typhus was probably given especially to typhus fever; it was generally applied to enteric fever as, in the beginning of the last century, these two affections, which in the eighteenth century were well differentiated by other names, were thrown together, so that a discussion lasting many decades was required to prove the non-identity of both, from a symptomatologic, anatomic and etiologic basis. Relapsing fever was brought into this group as it has some etiologic connections with typhus fever, in that its epidemics frequently occur simultaneously with typhus fever, so that, on this account, the necessity of separation of both only lately found general acceptance. In this manner, three diseases, differing in every respect, were artificially combined, and this has been maintained up to the present day, although now, as the etiologic principle of division for the infectious diseases has found general support, typhus fever is properly grouped with the acute exanthemata, enteric fever with cholera and dysentery, and relapsing fever with yellow fever. The matter has become so complicated that, in regard to the nomenclature, an unpleasant international confusion has taken place. In France, even during the third decade of the previous century following Louis, the name typhus has been retained for typhus fever, whereas abdominal typhus has been designated *fièvre typhoïde*. The English accepted this, whereas in Germany the old name proposed in 1759 by Sauvage, the originator of the term typhus, has been retained in nomenclature, both diseases having the name typhus, the difference being expressed in the adjective: typhus abdominalis and typhus exanthematicus. For the greatest majority of the physicians of Germany, as we shall see, typhus fever is an exotic disease not being known to the public at all, and, therefore, with us in Germany, by the profession and the laity, the name typhus is identical with enteric fever. The typhus of the Germans, therefore, is totally different from the typhus of the

French and English. It is to be hoped that this may be changed, but it is only possible if either the English or the French choose another name for typhus fever, for example, the old name spotted fever, lately recommended by Curschmann, or, if we accept for abdominal typhus the French name typhoid, or introduce another more in keeping with the actual condition. The latter would be more rational, for if the unhappy name typhus is to be preserved at all it belongs most properly to the disease which shows the typhoid symptom-picture most purely and most regularly. Naturally, great difficulties must be overcome with this, medical names that have become popular with the laity cannot be rooted out very readily, but these difficulties would not be unsurmountable; the introduction among the laity of the name typhus for enteric fever is not a very old result of professional endeavors.

Of the three typhoid affections, TYPHUS FEVER (typhus exanthematicus, spotted fever) has been known the longest; its appearance in murderous epidemics cannot be overlooked, and it is beyond doubt that many ancient descriptions of great pestilences relate to this disease. The old name for epidemic is pest, and among the pests of ancient times there have been many epidemics of typhus fever. This is maintained, for example, of the pest which decimated the population of Athens in the first period of the Peloponnesian war and Pericles is said to have succumbed to it. The correctness of the assumption of this fact is very likely, even if the description with which Thucydides has furnished us leaves many doubts. Also, there was probably many an epidemic of typhus fever among the pest epidemics of the middle ages.

The first description of the disease which is reliable was recorded in the beginning of the sixteenth century by Fracastorius in Verona; since then the affection may be followed up to the latest time. Its history is closely connected with that of the great European wars, it follows almost all movements of armies up to the present time; even in the last Turko-Russian war, the armies were decimated by typhus fever, and only the two wars of Germany in the second half of the previous century form an exception. War and typhus fever are so intimately related, that for the latter the names *pestis bellica*, *typhus bellicus*, *febris castrensis*, etc., for a time were in use, but epidemics of typhus fever are not alone connected with war, but also with famine which arises independently of warlike conditions, and this is frequently the signal for its outbreak. Among the epidemics of "hunger typhus," one stands out prominently, which, in the middle of the previous century, ravaged Great Britain and Ireland. In Ireland alone, a million cases were said to be observed. In Germany, after the cessation of the Napoleonic wars which flooded entire Europe with typhus fever, this affection had almost entirely disappeared, and as I have previously intimated, had almost disappeared from the memory of the physician. A famine occurring in upper Silesia gave rise to a great typhus epidemic, which has become especially celebrated because the youthful Virgil dedicated a minute observation of the same.

Still a third condition is said to be of importance in the genesis of spotted typhus, the massing of human beings in narrow spaces. The most prominent modern author of typhus fever, Murchison,¹ looks upon this as the most im-

¹ Murchison, *The Typhoid Disease*. Deutsch von Dr. W. Zülzer, Braunschweig, 1867.

portant factor in the production of typhus epidemics. Formerly, this factor was of greater importance than to-day; in prison, in ships, and in hospitals, typhus fever was a frequent visitor, and was designated as ship-typhus, prison-typhus and hospital-typhus. Nowadays, in civilized countries, in which the hospitals, and mostly also the prisons are more sanitary than the habitations of the poor, and in which, by the introduction of steamships, the conditions of shipping have undergone a complete revolution, these names are no longer justified. But the crowding of narrow spaces plays a rôle even to-day in the distribution of the disease; its principal nest is the habitation of the poorest, those without work and beggars. From these localities, the epidemics almost always take their start. On the other hand, nothing is clearer and less disputed in the etiology of typhus fever than its contagiousness. It is one of the most contagious diseases, and in this respect resembles the acute exanthemata, measles, scarlatina and smallpox. If this fact was ever doubted, this was only possible so long as typhus fever and enteric fever were not separated from each other. In those instances, in which we are dealing alone with typhus fever, the contagiousness stands out even more prominently than in the previously mentioned acute exanthemata, because the predisposition to acquire the affection is a general one. In small districts, in epidemics which are not greatly diffused, the contagion from case to case may be readily traced; however, in the large epidemics this is naturally impossible throughout as in the case of other contagious diseases. But even here, the contagiousness of typhus fever is particularly manifest. Only the most rigid measures of isolation can prevent the transmission to the healthy and to other, sick, inmates of hospitals. I may quote a personal experience in this respect. During the single great typhus epidemic in which I was concerned, I was physician in a hospital, the director of which, at the onset of the epidemic was convinced that typhus fever was not contagious, and for this reason the first patients that were brought to the hospital were not isolated. His convictions were soon corrected by the fact, that in all wards in which cases of typhus fever were placed, numerous transmissions to other patients occurred.

How great the contagiousness of typhus fever is further shown by the great frequency with which it is observed among the nurses, physicians, etc. Whereas in general, upon taking into consideration the previously described conditions of typhus fever, it is a disease of the poor, we may say of the most destitute, the well-to-do population suffer but slightly from it; physicians are an exception. In the previously mentioned epidemic with which I was concerned, all of the assistant physicians in the large hospital, with the exception of two, and a very great part of the nurses were attacked.

How are these etiological factors to be reconciled with one another? This question has been the subject of much discussion. Up to recent times, it was regarded as proven, that hunger, and especially the accumulation of persons within narrow spaces, could directly produce the disease, and a number of "substantiating" observations were brought forward to verify this. As long as it was not considered that this poison might be represented by a gas-producing body, there was no difficulty regarding this view. The "pestilential" smell which is generally present in breeding places of typhus fever was supposed to be an indication for the existence of this gas-forming poison and

of its genesis. Greater difficulty was encountered in the explanation of the transference of the disease from person to person. It was explained by a reproduction of the poison in the diseased body and the peculiar odor of typhus fever patients, to which I shall refer again later on, was supposed to be a point of support.

For us this hypothesis is untenable. Even for the prototype of miasmatic diseases, for malaria, it is proven that it is not produced by a miasma in this sense, but by a living organism. In such an exquisitely contagious disease as typhus fever there can be absolutely no doubt of this.

Naturally, up to the present, the exciting cause of typhus fever has not been successfully determined, although abundant efforts have been made. But this failure has been encountered in regard to the entire group of the acute exanthemata, in which typhus fever, with respect to its symptoms, has been counted for some time. It is remarkable enough that in just these exquisitely contagious diseases, the etiological conditions of which have furnished the material from which the existence of the contagium animatum has been concluded by deductive methods, the actual proof of the same has given rise to insurmountable opposition. This is either due to the fact that the exciting cause of these very contagious diseases is characterized either by their especial diminutiveness, thus evading our observation, or that they belong to a group of microorganisms which differ so greatly from the known causes of disease that the methods which have been developed for their recognition are insufficient.

However, I must not conceal the fact that still a not inconsiderable number of actual facts regarding the nature of the causative factor of typhus exanthematicus have been obtained. But we do not gain from them the conviction that the microorganisms that have been discovered are the actual causes of typhus fever. Of the most of them, we may say from the onset, that they are for the greatest part only secondary elements. Most plausible are the communications of Lewaschew¹ who found, particularly in the blood of the spleen of living typhus fever patients, peculiar motile formations that had spirilli-like processes. Organisms, as also processes, may be stained in a living condition, by basic dyes, whereas the processes in dry preparations cannot be stained. Lewaschew also succeeded in producing cultures; these are the microorganisms to which he has given the name spirochaete exanthematicum; in regard to their culture media, they are very selective. He believes that the organisms almost simultaneously discovered by Thoinot and Calmette² are identical with his, and correspond to the involution forms which he has seen. A year later Dubieff and Bruhl³ no longer found these microorganisms, but in their place diplococci were found, but only in the blood of the cadaver; prior to death they were found in great quantities in the pharynx, larynx and lungs. A repetition of these tests by Spilmann⁴ could not substantiate this. Also Balfour and Porter,⁵ the latest authors in this realm of investigation, have had negative

¹ Deutsche med. Wochenschr., 1892, Nr. 13 u. 34.

² Annales de l'Institut Pasteur, 1892.

³ Arch. de méd. expérimentale, 1894, Nr. 2.

⁴ Arch. de Méd., 1896, p. 619.

⁵ Edinb. Med. Journ., 1900.

results, as the diplococci discovered by them in the blood also occur in other diseases.

Therefore, a positive result of these investigations cannot be maintained, but we cannot doubt that the exciting cause of typhus fever is due to an animate body as is the case in the acute exanthemata.

Does this put aside the view of a spontaneous development of typhus fever without further consideration? Can typhus fever arise without being directly or indirectly due to another case of this affection? I believe that *a priori* this must be looked upon as impossible. Naturally, if the pathogenic action of the organism of typhus fever is looked upon as an unchangeable property, this assumption would presuppose conviction; if, on the other hand, we believe, with the French investigator Kelsch,¹ that in general, the exciting cause of typhus fever is a harmless microorganism which only takes on its pathogenic properties, this explanation has no difficulty under the conditions which have been named above.

We should only recur to this if it were absolutely certain that the spontaneous development of typhus fever cases had been proven. In my opinion this is not the case. The points which are advanced in support of it are nothing more than those which are met with in the other contagious diseases. And we shall finish with this, for the sufficient reason that it is not always possible to follow the tortuous paths of the transmission by the sick and their effects in the individual case. Usually in all of these cases there are assurances that the sick have no opportunity of coming into contact with the previously mentioned conditions. These assurances, however, are most often faulty, and are insufficient to serve as a basis for weighty scientific conclusions. Just this condition has been shown in the case of typhus fever. One of the most marked examples of the spontaneous development of the typhus fever germ upon an overfilled, unclean ship, was the story of an Egyptian frigate which in the year 1861 brought typhus fever to Liverpool, although it came from a country free from typhus fever and there were no cases on board. A further investigation of the situation, however, showed that among the crew there was typhus which had not been diagnosticated, and that some of these patients had shown severe symptoms at the time in which they embarked.²

Therefore, in the case of typhus fever, there is no necessity to fall back upon complicated hypotheses, and I assume, with the most modern authors, that the causative agent of typhus fever is only transferred by means of the sick and his effects. That the latter play a great rôle is shown by the numerous cases which occur among laundresses and disinfectors. It may also be assumed for typhus fever, as well as for other eruptive diseases, that the contagious principle adheres to the rooms occupied by patients, and may retain its activity for a long time; how long, has not been decided, we only know that air and sunlight have a great influence and that where they are absent the contagious principle may remain active for many months. It is clear without further explanation that, under these circumstances, the method of transmission is as difficult to follow as in the case of measles, scarlatina and variola.

¹ Kelsch, *Traité des maladies épidémiques*, Paris, 1894, p. 504.

² Thoinot, *Typhus exanthématique*. *Traité de Médecine par Charcot, etc.*, Tome ii, p. 11.

If the view regarding the spontaneous development of typhus fever is dropped and we adhere to the opinion that, similar to the other acute exanthemata, typhus fever is produced principally by the sick person and everything that originates from him, these factors which I have emphasized in the etiology are not causes of the disease, but causes of its epidemic distribution, in that they favor the possibility of contagion. War and the massing of individuals unquestionably show this action, but this does not exhaust the etiology of typhus fever for these factors play a very different part in this affection from what they do in the other contagious diseases. It must be assumed that the contaminated air of overfilled rooms and the ill-smelling gas-formations that are contained in them increase the predisposition to the transference of the disease. This is also unquestionably true for the under-nutrition of the human beings, which is produced by hunger and poverty; bodily and mental exertions have also been looked upon as predisposing factors, and have been made responsible for the numerous cases occurring among the well-to-do and well-nourished physicians and nurses. I believe this to be questionable, the satisfactory explanation of this fact may be found in the great contagiousness of the disease alone; in the typhus fever epidemic observed by me, the very busy assistant physicians in the surgical division were not attacked even when compelled to do night duty in the typhus fever ward.

It is shown in the epidemics that the predisposition is a very widely distributed one, and that the various morbidity statistics furnished by different modes of life, age, sex, are explained by their different possibilities of contagion. An actual slighter predisposition appears only to exist with nurslings. It has been further maintained, that certain occupations confer protection from the contagion, especially those of butchers, canners, candle-makers, but this must not be looked upon as absolutely certain.

Like all acute exanthems, typhus fever also conveys a high degree of immunity to those who have recovered from it; this usually lasts for life, but there are rare exceptions, some having acquired the disease twice, even three times.

In which epochs, and how long is the disease contagious? It is certain that transmission to the well may occur during the entire course of the fever, whether this already occurs in the stage of incubation, and is still possible in convalescence, has not been determined with certainty.

Even if the contagious principle cannot be a gas, it is still probable that it is contained in the air, and the transmission occurs, and is likely in all acute exanthemata, by inhalation. This is, however, not generally accepted. There are still authors who regard direct contact with the sick person as the only possible method of contagion. I do not believe this to be correct. There are many examples of transmission in which direct contact can be excluded. I do not wish to relate individual experiences, in which it may always be doubted whether they have been correctly interpreted and carefully reported, I would rather mention a number of mass infections which have played a great rôle in the history of typhus fever. These are the so-called black assizes, cases in which the accused was brought from pest prisons into the full court room, and a greater part of the judges and listeners were attacked. Six examples of these black assizes have been reported in the course of more than two

centuries. Under these circumstances, the correctness of the fact cannot be doubted, and in these cases a direct contact may certainly be excluded.

On the other hand, it is certain that typhus fever hospitals are not dangerous to the inhabitants of the surrounding houses and this is a fact which has always been brought forward against the view of the transmission of the poison by the air. It only proves, that in the open air the infectious principle has been rendered harmless, and, in fact, it has been shown that physicians and nurses are less susceptible to contagion the better the ventilation of the wards, and that this danger does not exist at all in the treatment of typhus fever cases in the open air.

In what form the contagious principle finds exit from the body, whether by the scales of the skin or by the expectoration of the patient, has been as little determined as in the other eruptive diseases.

I have previously mentioned that we must differentiate between the epidemic and the endemic appearance of typhus fever. This is also more or less the case in all acute exanthemata, but there are still very pregnant differences between typhus fever and the other acute exanthemata in this respect. In measles, scarlatina, etc., the limitation of the endemic area, in which these affections never die out, is easily comprehensible. These are the centres of communication, the large cities. In variola, another factor is determining, the influence of a more or less complete protection by vaccination; in typhus fever, however, distinct geographical districts are to be regarded in which the disease never dies out, and from which points mostly from the influence of the above-described calamities affecting the people, it takes its epidemic course in other countries, in which regions, as a usual thing, the disease is unknown. In this method of distribution, contagion may be distinctly recognized as the determining factor. Countries and provinces which border upon the extended endemic area are mostly threatened, and, on this account, are primarily in danger of importation. Thus, in the times of peace in Germany, especially the eastern provinces are attacked by typhus epidemics, which border upon Russia, in which country the disease prevails endemically in widely distributed areas, whereas Great Britain with its typhus epidemics is under the influence of Ireland, which is to be looked upon as an endemic focus of typhus fever. The determining factor of these endemic typhus fever countries has not been definitely fixed, probably in the mode of life and the conditions of living of the working population. Regarding the extension and number of the endemic typhus fever areas, we are still not sufficiently informed. It is certain, that for a long time we have decidedly underestimated them, and this gave rise to the difficulty in the explanation of numerous apparently spontaneously arising epidemics which have led to the assumption of the spontaneous development of the typhus poison. In fact, the greatest number of the countries of Europe have endemic typhus fever areas: Germany, Upper Silesia; France, as was recognized in the last Paris epidemic, Bretagne; also Austria, Turkey, and Italy are not free from typhus fever. Of non-European countries, North Africa, Persia, and China are to be mentioned. Also, the disease appears to be endemic in tropical regions; from one of my former assistants, I know, for example, that in Mexico it exists year in and year out, under the old Spanish name of *tabardillo*, a designation which has been borne by typhus fever since

the conquering of Granada by the Spaniards, it having been thus described. Under these circumstances, there is always sufficient material for transmitting the disease, and we will have all the less cause to assume a spontaneous development of the typhus fever contagion with the observation of these facts.

ETIOLOGY OF RELAPSING FEVER

The etiology of the second infectious disease from the group of typhoid diseases is connected in many ways with that of typhus fever. Relapsing fever, *febris recurrens*, is a disease which has also probably existed for a long time, but which cannot be followed historically further back than the eighteenth century. At first it was looked upon as a less severe form of typhus fever; only in the middle of the last century has it become clear that we are dealing with two basically different affections, the epidemics of which, however, frequently arise together, crossing in manifold ways. The reason for this may be looked for in the fact that the same influences which are determining for the development of typhus fever epidemics, which we have learned to recognize, are also of importance in relapsing fever, only that in the latter want and famine are of greater importance than the close housing of human beings; whereas relapsing fever is also a species of hunger-typhus, it does not occur as ship-typhus, prison-typhus, etc.

In those regions in which relapsing fever and typhus fever arise together, the proportion is always such, that at first a pure relapsing fever exists, or that the cases of relapsing fever are in great majority; gradually the typhus fever cases increase more and more until finally they form the majority. Even in times when both affections were not sufficiently differentiated, this condition could be recognized. The mortality of relapsing fever is a much lower one, and this shows itself in that the severity of the epidemics and their duration appears to constantly increase. Partly this course of the epidemics may be explained in that the convalescents from relapsing fever have a greater predisposition to typhus fever infection, so that not rarely the typhus fever affection is immediately connected with relapsing fever, whereas the opposite condition has never been observed.

Relapsing fever is also a contagious disease which unquestionably is transmissible from man to man. Besides this direct transmission, for a long time spontaneous development of the infectious principle has been assumed, besides the previously-mentioned conditions. The proofs of this assumption are no more forcible than in the case of typhus fever, whereas the propagation of the affection by contagion is even more conspicuous. In the case of relapsing fever, the previously-mentioned deleterious effects do not produce the poison of the disease but, by favoring contagion, the epidemic distribution of the disease is increased. Failure of crops, and famine due to this cause, force country laborers into the city; industrial crises are the cause of the return of the factory workers to the country, and simultaneously force a more or less large percentage into the class of the idle and vagabonds, who, collecting in the worst quarters, represent the principal contingent for the development of the disease. Relapsing fever is a disease of the poor, even to a greater extent

than is typhus fever. Those in better circumstances are only attacked by the infection in so far as their occupations give rise to contagion, such as in the case of physicians and nurses. The contagiousness of relapsing fever is decidedly less than that of typhus fever; the number of hospital infections is much smaller. I was concerned in an epidemic of relapsing fever in which the patients were not isolated; even this circumstance shows that there is a great difference between the contagion of typhus fever and of relapsing fever. Either the predisposition is present to a slighter extent or the process of contagion itself is a more difficult one.

In replying to this etiologic question, in a case of relapsing fever, we are not so completely in the dark as in the case of typhus fever, because the exciting cause in this instance is known to us. Obermeier,¹ in the year 1873, discovered in the blood of relapsing fever patients, fine corkscrew-like, wound, thready structures in constant motion, which morphologically resembled the spirilli found in the mucus of the gums and in putrid pulmonary affections. After years of disappointing experiments, this was the first proof of a micro-organism in a contagious disease of man. How skeptic the profession at that time regarded such findings is shown by the great reluctance with which Obermeier communicated his discovery to the Berliner Medicinischen Gesellschaft, Feb. 26, 1873, as well as by the remarks of the presiding officer Langenbeck. Nevertheless, it soon became clear that the spirilli of Obermeier were actually the cause of relapsing fever. The close connection between their appearance and the morbid phenomena to which we shall recur later on, alone make this more than likely. However, the inoculation experiments are conclusive. The spirochetæ of Obermeier cannot be transmitted to our ordinary trial animals, but the inoculation into apes produces a usually milder and briefer disease, which is analogous to that occurring in man. In man also, successful inoculations have been made, these were partly accidental ones, some individual investigators—Münch and Metschnikoff—have inoculated themselves; finally, a Russian physician—Moczutkowski² did not hesitate to transmit relapsing fever to healthy human beings; fortunately, in these experiments no fatal cases occurred. It was found that only the blood of the affected transmits the disease, whereas the secretions and excretions which originate from spirilli may be inoculated without producing effects. This in itself would not be an absolutely certain proof of the importance of spirilli as the exciting cause of the disease, as also other not visible infectious materials might be transmitted with the blood and an isolation of the spirilli by culture has not been successful. But it has been shown that only the blood during the febrile stage was active, and as the spirilli are only found in the blood during the fever stage, their functions as the exciting cause of the disease may be looked upon as certain. It is true, the proof of spirilli was not always possible at the onset of the disease, occasionally in the affected blood. This may be due to the fact that if spirilli are few in number they can only be found with difficulty.

What then is the natural mode of infection? In stating previously that

¹ Berliner klin. Wochenschr., 1873, Nr. 13, p. 152.

² Centralbl. f. med. Wissenschaften, 1876, Nr. 11.

the disease is transmitted exclusively from the sick to the well, this must be complemented by the statement that the contagion may also be transmitted by effects (fomites) of relapsing fever patients. We also know that to contract the disease, direct contact from person to person is not necessary, whereas, on the other hand, the infectious principle does not show a great tendency to act at a distance. In the Breslau epidemics it was observed that in lodging places of vagrants the disease slowly advanced from bed to bed, usually first infecting the occupant of the neighboring bed.

All these properties of infection become plain if we assume that the natural process of transmission is inoculation, which, by means of clothing and beds in which parasites are contained—bed-bugs and fleas—is transmitted. This hypothesis, which Klebs had proposed some time previously, has been made likely by the proof which was furnished by Tictin,¹ that in the digestive canal of bed-bugs found in the beds of patients with relapsing fever, spirilli were present and that the inoculation of the blood obtained by crushing the bugs produced the disease in apes. These tests are not absolutely convincing, the proof is still missing that the bite of bed-bugs produces the disease, that by this means a sufficient quantity of blood containing spirilli enters the body that is to be infected; but it is still very likely, as in the previously mentioned infections of man, acquired at autopsies, for it is hardly possible that large amounts of the infective product could have been transmitted. Another mode of infection mentioned by Tictin is this, that during scratching, blood from the crushed bed-bugs reaches the wounds produced by the scratch. Regarding the importance of fleas in the contagion, no actual material is at our disposal, neither do we know whether a transference by mosquitoes is possible.

This hypothesis alone is sufficient to allow us to understand that these very frail spirilli are transferred from the blood of the sick to that of the well. Formerly it was assumed that a transmission occurred by the air, this being due to the agency of spores, but we have not the slightest points of support for the existence of such durable forms. Further, this hypothesis best explains the peculiarities of the relapsing fever infection: the development of epidemics in the unhygienic sleeping abodes of vagrants and those out of work, the slight tendency to contagion in clean hospitals, the contagiousness solely during the febrile stage, the tendency of those in the neighboring beds to contagion without a direct contact between the sick and the well, the transmission by fomites and effects of the sick, etc.² In other respects, as has been mentioned, the epidemiologic conditions of relapsing fever are very similar to those of typhus fever. For the former affection there are also endemic districts. Our knowledge regarding them is by no means conclusive as yet, but we may say that the endemic distribution of the disease does not equal that of typhus fever. In Europe, only Ireland and Russia are to be looked upon as

¹ Centralbl. f. Bakteriologie, etc., 1897, Bd. xxi, p. 5.

² This mode of transmission hardly comes into question in the case of typhus fever. I have previously called attention to those experiences, showing that this affection may be carried to decided distances, therefore, may be transmitted by the air, and, apart from this, inoculation experiments which were made by Moczutkowski with the blood of typhus fever in human beings have not been successful.

endemic districts. In the epidemics which have repeatedly passed over Germany in the last decade, the importation from Russia could always be proven, whereas in case of most of the epidemics of England and Scotland, it is certain that they were of Irish origin.¹ In keeping with this, in Germany principally the provinces which border upon Russia—Silesia, Prussia and Posen—have been affected by relapsing fever epidemics; Brandenburg (Berlin) and Pomerania have been repeatedly infected from these districts. The last epidemic—1878 to 1880—distributed itself in an easterly direction over a large part of Germany. In the development of these epidemics, it could usually be determined that primarily, principally travellers were affected, the affection thus arising in the lodging houses of these travellers and gradually spreading to the inhabitants of the district. Besides Europe, we must look upon Egypt and India as endemic districts, but here our knowledge is especially incomplete.

All other etiological moments are greatly inferior to those which have been mentioned. Regarding sex, the male sex is affected to a much greater extent than the female, but only in so far as the opportunity for contagion is greater in them. Regarding age, the greatest contingent is shown during strong adult life, probably for the same reasons. Only in sucklings, as in typhus fever, there is a relative immunity, but cases have been reported during the first year of life.

Occupation does not confer immunity. That the disease spares the well-to-do classes in general has already been mentioned, and also that an explanation of this fact does not require the assumption of a difference in predisposition. Neither do various physiological or pathological conditions influence the predisposition. Even recovery from the disease does not markedly diminish it, or if at all, for a brief space of time only; second attacks have been observed even a few months after recovery from the disease.

The influence of the seasons and that of various climates regarding the appearance and distribution of relapsing fever have not been noted.

SYMPTOMATOLOGY OF TYPHUS FEVER

Symptoms.—Clinically, typhus fever characterizes itself as belonging to the acute exanthemata. In spite of the variations which may be due to the differences in intensity of the affection and the manifold complications, the fundamental clinical picture is always retained. This refers to the eruption which appears in the first week of the disease, and if, in spite of this, typhus fever is not reckoned as belonging to the acute exanthemata, it is probably due to the fact that very often the eruption is not very prominent, that the fever does not disappear after the eruption is complete, and that in the course of the disease the severe cerebral phenomena are so predominant that they primarily receive the attention of the physician. In the sixteenth century typhus fever was frequently confounded with measles, and the authors of that period devoted entire chapters to the differential diagnosis of both diseases.

¹ In one of the last epidemics in London, this was due to the importation on the part of Russo-Jewish emigrants.

The clinical picture of typhus fever may be divided into the same stages as those of the acute exanthemata. Naturally, it must not be forgotten in this instance, as little as in the other, that all such divisions are artificial, and are more or less arbitrary.

The duration of the period of latency of typhus fever, upon the average, amounts to nine days, in the majority of cases deviations from this general figure amount to but a few days, but there are observations also of a very short or of a very long period of incubation—a few hours and many months. If we reflect how difficult it usually is in an epidemic to determine with certainty the exact moment of infection, we will become very suspicious regarding these observations.

The period of latency is usually a very complete one, only exceptionally are mild febrile corresponding symptoms observed.

The disease itself begins very suddenly, usually with a severe chill, rarely with several chills of slighter intensity. The temperature rises rapidly, scarcely falls upon the next morning, and usually even upon the second evening shows a high febrile range. Corresponding to the temperature, the pulse frequently also rapidly rises. Very quickly a sensation of a grave impending disease sets in, which almost always even upon the first day causes the patient to take to his bed. The physician finds him with a reddened face, due to fever, hot, dry skin, frequent, soft pulse, injected conjunctivæ, with a thickly coated tongue, this coating often already of a brownish color, inclining to dryness, and severe, disturbing thirst. The great lassitude and weakness is conspicuous, already upon the first day movements are tremulous. Pains in the small of the back and limbs, severe headache, vertigo, tinnitus aurium, agonizing insomnia, hoarseness and dry cough appear, also nausea and vomiting. The bowels are usually constipated, the abdomen, however, remaining soft, not sensitive to pressure, and usually, even in the first few days, enlargement of the spleen may be determined. Even during this time the mind of the patient is no longer normal; during the day he may still be rational, but the great apathy and the somewhat stupid expression of the face are conspicuous; at night delirium occurs, the brief, interrupted sleep is disturbed by weird dreams, and also while awake very frequently delirium can be noted.

All of these symptoms of the prodromal or stage of invasion increase up to the time of the development of the exanthem, which occurs between the third and seventh, most often upon the fourth or fifth day, being frequently accompanied by a slight fall in the temperature, which may also frequently be absent. The exanthem consists of red macules, varying in size from a pin's head to a lentil, which scarcely arise above the level of the skin, disappearing upon pressure with the finger. The eruption is first noted in the flanks, the shoulders, the anterior wall of the axillary cavity, and distributes itself from there, inside of the next two days, to the chest, shoulders, and extremities, being especially prominent upon the flexor surfaces of the forearm; the neck and face usually remain completely free from the eruption. Besides these superficial efflorescences, there are found still deeper, less distinct points which are called subcuticular mottling. In the regions in which this eruption is the most copious it causes a livid marbling of the skin, which is very characteristic of typhus fever.

The nature of the eruption is, therefore, that of the acute exanthemata; it is completed in a few days, whereas in enteric fever the roseolar eruption occurs in repeated crops during the greater part of the duration of the disease. The profuseness of the eruption and its distribution over the greatest part of the body is also in keeping with the acute exanthemata. It is true, this varies more in the case of typhus fever than in the case of the other eruptive diseases; cases without eruption frequently occur and still more frequently has a rudimentary development of the eruption been observed. On the other hand, the exanthem is sometimes so copious that confluence takes place, it then resembles measles so closely that it is described as measly or rubeolous.

Prodromal eruptions—transitory erythematous reddening of the back, the neck and chest—is also reported; perhaps in this category belongs a large flaky exanthem upon the dorsal surfaces of the hands and forearm, which has been observed upon several occasions, and which disappears and reappears repeatedly. This is also found in the eruptive stage besides the actual exanthem of typhus fever.

The completion of the eruption—and this is one of the marked differences compared to the acute exanthemata—is by no means the signal for an improvement in the phenomena of the disease. On the contrary, now the malignant character of the morbid picture begins to develop itself. It is true, the complaints of the patient cease, but the mind becomes more and more cloudy, he begins to be delirious during the day.

The delirium itself is of very varying intensity and differing character, occasionally it is quite low, muttering (the typhomania of the older physicians), occasionally it is furious, the patients jumping out of their beds, attempting to run away and they do escape if they are not watched, they may attempt self-destruction, injure themselves, jump out of the window, or attack their nurses or the patients in neighboring beds (delirium ferox). These unconscious actions are naturally the outcome of very varying delusive conditions, usually of a tormenting character. The remembrance of these does not completely disappear in convalescence, and we are frequently in possession of descriptions by prominent physicians of some of their own hallucinations.

The prostration of the patient increases more and more and is most noted especially after such attempts at force. The tongue becomes dry and fissured, sordes collect upon the lips and teeth, the breath becomes fetid. The pulse becomes more rapid, small and softer. The exanthem becomes darker, no longer completely disappearing upon pressure with the finger, and the petechial transformation occurs in it. The centre of the macules becomes purplish and bluish-red, whereas the periphery takes on a brown color. This petechial transformation only affects a minority of the efflorescences, persisting then into convalescence, whereas the other eruptive areas rapidly become pale and disappear. Actual petechiæ, i. e., cutaneous hemorrhages which occur independently of the eruption, are only exceptionally found.

This division of the clinical picture has been described as the stage of excitation, this being followed by the stage of depression; the delirium declines more and more, coma taking its place. The patient lies upon his back, helpless and immovable, with a stupid facial expression, muttering incomprehensible words; occasionally he is silent, scarcely responding to a call, with trembling

hands which are moved by subsultus tendinum, there is also carphologia. The conjunctivæ are deeply injected, the pupils are contracted. The pulse is frequent, small, scarcely perceptible, often intermittent. The temperature remains high, and the skin is less dry, the peripheral portions becoming cool. Constipation has continued or has given place to diarrhea; feces and urine are involuntarily voided into the bed. Even with the best nursing, the sacral region becomes red, showing a tendency to bed-sores, which may become gangrenous. In this stage the coma of the patient is not complete; in reference to this, we are also in possession of observations of prominent physicians upon themselves, in which they have described the tormenting deliria of these days.

In this manner the patient has reached the second half of the second week of the disease, his condition has become almost desperate, the fatal issue appears to be immediate, and, as a matter of fact, frequently does occur during this period. However, in the majority of cases, an abrupt change now takes place. Typhus fever terminates by crisis between the tenth and fourteenth, usually about the twelfth, day of the disease. This crisis manifests itself principally by an abrupt change of the symptoms. The patient falls into a quiet sleep lasting for several hours, from which he awakens completely changed. The physician who on the evening prior has left him as one almost dying, finds him the next morning still somewhat delirious and confused but yet in possession of his senses, with a cool skin, slow, full pulse, and a tongue becoming moist; however, markedly debilitated and weak to the greatest degree. This change in the condition of the patient goes hand in hand with the critical defervescence of the temperature, which naturally is not so abrupt as the other symptoms, but, nevertheless, it is a critical fall of temperature, which either occurs in one bound, or which may be interrupted by a slight rise; however, within twice, or at the most three times, twenty-four hours, the temperature returns to normal.

Only very rarely does a defervescence by lysis occur. The critical accompanying phenomena—sweating, sediment of urates in the urine—are not absent but are not very prominent.

The severe disturbances of the general condition which precede the crisis are frequently in keeping with the rise of the temperature, this being a pre-critical rise. The temperature of the body, which during the entire course of the clinical picture showed a severe type of a continued fever with very slight morning remissions, amounting for the most part to about 104° F., then rises above 104° F., even to 106.5° F.; in keeping with this the pulse frequently rises to 140. More rarely does a pseudocrisis precede the crisis or an ambibolic stage lasting several days.

The crisis is followed by convalescence. At first the patient is very weak, the mind is somewhat clouded for days, the pulse gradually returns to normal, and frequently shows an epicritical bradycardia. Soon the desire for food arises, and with a plentiful administration of nourishment, strength returns surprisingly rapidly.

This stage of convalescence reminds us of the acute exanthemata in so far as here a small, flaky desquamation is observed. This becomes especially conspicuous and demonstrative if, as is frequently the case, sudamina occur toward the end of the disease.

From this picture of a severe case of typhus fever which, however, runs a favorable course, there are many deviations, due to differences in the intensity of the infection and also due to numerous complications.

Primarily, there are the severe cases which at the acme of the disease, without complication and only by the intensity of the toxemia, terminate fatally.

Death commonly occurs toward the middle of the second week, but in especially severe cases it may take place earlier, even at the end of the week. In especially severe epidemics, fatal cases occur in the first few days (typhus siderans). Prior to death the soporous condition, which has been previously described as the period of depression, increases to deep coma. The patient cannot be aroused at all, appears to look into space, and has a cyanotic face and ice-cold extremities (coma vigil). Death frequently announces itself by a preagonal, hyperpyretic rise of temperature, rarely by an abrupt fall of the temperature, with an increasing pulse frequency.

The autopsy finding in such cases shows little that is peculiar. The absence of specific localization, as, for example, the intestinal changes in enteric fever, forms the most important characteristic of the same. The anatomical changes are those which are found in all severe infectious diseases, and are more or less well developed. The only thing that is specific is the residue of the efflorescences which have become petechial, and are occasionally still visible in the cadaver. Apart from this there are found:

I. Dark, feebly coagulating blood, the exact examination of which, according to modern methods, is still indefinite, even during life.

II. Dark, dry musculature, which shows the not very advanced changes of Zenker's degeneration.

III. A dilated heart, with flaccid, friable musculature, the exact changes of which have not yet been accurately studied.

IV. Catarrhal changes in the mucous membranes of the nose, pharynx, larynx, and bronchi, which sometimes increase in the larynx, showing deep processes which resemble the typhoid ulcer of enteric fever and its consequences. Further, atelectasis and hyperemia of the lungs, frequently broncho-pneumonic areas of consolidation.

V. Enlargement of the spleen, with soft friable tissue. Not rarely enlargement of the spleen is absent, this is the more common the later death occurs.

VI. Hyperemia of the liver and kidneys, with swelling and cloudiness of the parenchyma.

VII. No specific changes in the digestive canal and in the mesenteric glands.

VIII. Hyperemia and edema of the central nervous system, increase of the cerebrospinal fluid, without inflammatory changes of the same. Other anatomical changes will be described among the complications.

In contrast to these severest cases, which are distinguished from the onset in that all disturbances, the febrile phenomena as well as the cerebral symptoms, are very marked, are the extraordinarily mild cases.

Primarily, a condition must be described that may be recognized in physicians and nurses, that are busy for months with typhus fever patients

without acquiring the disease. They complain of general malaise, slight fever, anorexia, disturbed sleep. If they leave the typhus atmosphere these phenomena disappear. The French author Jacquot,¹ who has described such cases and has designated them as “typhisation à petite dose,” a name which signifies their very questionable interpretation.

Further, there are observed during epidemics of typhus fever, febrile attacks of brief duration without eruption, which have been looked upon as abortive types. Naturally, the interpretation of these is also very questionable.

Certain abortive cases are such in which the affection begins with all, often of very severe, symptoms, and, a few days after the development of a more or less copious exanthem, defervescence takes place.

During defervescence, as also not infrequently during the crisis, herpes facialis occurs. Besides this, there are still cases which show the regular course of the fever of typhus fever, in which, however, the fever itself and all other symptoms are very mild. Especially are the severe cerebral disturbances absent in them, the tongue scarcely becomes dry. These mild types of typhus fever are found especially frequently as sporadic cases, but there appear to be also epidemics in which they predominate. I remember that R. Köch told me of such an epidemic which he observed in Wollstein.

Numerous *complications* influence the symptom-picture of typhus fever. For the most part this is due to *mixed* and *secondary infections*. It appears as if other epidemic diseases may be simultaneously present with typhus fever in the human being. This has been observed upon several occasions in the case of true dysentery which, for example, occurred simultaneously with typhus fever in the Crimean war; occasionally variola, scarlatina and erysipelas have been simultaneously present. This has also been maintained of diphtheria, and, in fact, it appears, that the pseudomembranous affections which arise from the nose and pharynx affect the larynx and bronchi, and in a very typical manner produce the phenomena of stenosis of the larynx.² Even if the bacteriological examination of such cases has not been determined, it is nevertheless plausible from the anatomic conditions, that the case in question is true diphtheria. Less likely, on the other hand, is the combination with scurvy maintained by the older authors.³ In these cases it is probably the most severe action of the typhus poison giving rise to the hemorrhagic form of typhus fever. Occasionally, as in the case of purpura variolosa, the hemorrhagic diathesis appears in the first days of the disease, at times even before the appearance of the exanthem. Cutaneous and mucous membrane hemorrhages, hemorrhages from the nose, the gums, the pharynx, with ulcerating necrosis of the mucous membrane, hematuria, with hemorrhagic inflammation of the pelvis of the kidneys, and of the bladder, severe hemorrhagic nephritis, gastric and intestinal hemorrhages occur and, with a falling temperature, rapidly lead to the fatal issue. The cases that show a less fulminant course are also almost always fatal; they show from the onset severe phenomena of infection, the eruption early becoming petechial and being widely distributed; many true petechiæ are also noted; besides nephritis there is often found hematuria, and gastric and

¹ Jacquot, Du typhus de l'armée d'Orient, Paris, 1856.

² Salomon, Deutsches Archiv f. klin. Med., vvxii, p. 476.

³ Murchison, loc. cit., p. 167.

intestinal hemorrhages. Now and then such hemorrhages from the intestinal tract without ulcerative processes are the only expressions of the hemorrhagic diathesis. Intracranial hemorrhages also occur under the symptom-complex of apoplexy, but this clinical picture may also occasionally arise from thrombosis of the cranial arteries.¹

Among secondary infections, there are primarily to be mentioned the suppurative ones. As the means of egress of the pyogenic organisms, besides the dry mucous membrane of the mouth, of the tongue, of the pharynx, which show fissures and tears, the bed-sore must be considered, which in processes that are severe and of long duration, occasionally causes great destruction, due to pressure of the parts in question. The purulent infection gives rise to the well-developed symptom-complex of general pyemia, with chills, jaundice, purulent arthritis (we occasionally observe endocarditis, which also probably belongs to this category), as well as more localized suppuration. Among the latter there are to be included abscesses of the subcutaneous tissue and the lymph glands, purulent meningitis,² which has been observed several times, and a case of abscess of the brain.³ By the entrance of pyogenic organisms from the oral cavity, the not infrequent complication of suppurative parotitis may be explained, which often also threatens life even in convalescence; by invading the pharynx, the comparatively frequent purulent affections of the middle ear, which mostly arise in convalescence develop, causing transitory disturbances in hearing. The skin serves as a port of entrance for the development of furuncles, which often arise in convalescence. In so far as bacteriological examinations of these purulent processes have been determined, they were constantly due to staphylococci.

Very frequent *complications* of the disease are those on the *part of the lungs*. According to their anatomical appearance, they are true fibrinous pneumonias. They mostly occur in the second week, the symptoms differing but slightly from the severe clinical picture already present, so that only the physical signs allow of their recognition. Besides this, as has already been mentioned, bronchopneumonia occurs, often due to aspiration into the air passages of substances intended for the mouth and pharyngeal cavity. The severe mental condition favors the development of these processes, and, on the other hand, covers their consequences to such an extent that the clinical picture is scarcely influenced by them; they frequently lead to a gangrenous destruction of the pulmonary tissue and are probably the most common source of the not infrequent pulmonary gangrene in typhus fever. Especially, it is said that the aspiration of ichorous pus from perichondrial abscesses, which occurs in connection with the previously mentioned ulceration of the larynx, is the cause of pulmonary gangrene.⁴ Besides gangrene of the lung due to aspiration, there are also other foci of mortification produced by the entrance of ichorous thrombi, and this view is favored by the coexistence of pulmonary gangrene and gangrenous bed-sores. To the various forms of disease of the

¹ *Hampeln*, Ueber Flecktyphus. Deutsches Archiv f. klin. Med., xxvi, pp. 243, 244.

² *Hampeln*, loc. cit., p. 243.

³ *Taussig*, Gehirnbrabscess im Anschluss an Flecktyphus. Prager med. Wochenschr., 1900, Nr. 24.

⁴ *Salomon*, loc. cit., p. 477.

lungs, pleurisy may be added which, according to the nature of the pulmonary process, may be either serous, purulent, or ichorous.

The *renal affections* which complicate the disease are to be regarded solely as the direct consequences of the typhus fever affection. The more intense the disease, the more severe the implication of the kidneys. Slight albuminuria, with excretion of small amounts of casts and renal epithelium, is very common in typhus fever. These phenomena disappear with the onset of convalescence. Occasionally a mild renal affection increases to a severe nephritis, albumin, casts, and epithelia are excreted in large amounts; frequently there is an admixture of blood in the urine. The majority of these cases lead to death; the reports of the anatomical changes of the kidney are scarce. If the patients recover, the nephritis lasts beyond the febrile process, but the condition gradually improves. Dropsical phenomena are not observed in these renal inflammations, however, uremic convulsions are by no means rare.

Comparatively frequent in typhus fever is *spontaneous gangrene* of the extremities, the cause of which may be properly looked for in the inflammatory affection of the arteries and their secondary thromboses, being a parallel process to the previously mentioned thrombosis of the cerebral arteries with consecutive softening of the brain. As is usual in this condition, previous to the appearance of mortification, severe pains occur in the affected extremity, combined with coldness, lividity, disturbances in motility, and disturbances in sensation.

Less clear regarding its genesis, is the appearance of gangrenous areas at the tip of the nose, the borders of the concha of the ear, the penis and the scrotum, which are occasionally observed in severe affections. The mortification of these parts is referred to cardiac weakness due to insufficient circulation. Noma, which is now and then observed in typhus fever of children, is certainly a mixed infection.

Finally, *paralyses* must be mentioned which occur as sequels of typhus fever. Investigations regarding their anatomical basis are missing but, unquestionably, they are due to the usual forms of infectious polyneuritis. Murchison¹ has already described a severe case of this kind, which showed a complete typical symptom-picture of polyneuritis. It may lead to severe muscular atrophies but usually, after existing for months, complete improvement occurs. It should be mentioned, further, that myelitis was observed once in a fatal case of typhus fever, whereas in two other cases running a favorable course, spinal phenomena occurred *intra vitam*.²

As in most infectious diseases, these numerous complications vary in different epidemics. Each then attains thereby an individuality, on the other hand, the typical clinical picture of the disease, in spite of the complications, is usually well characterized.

SYMPTOMS OF RELAPSING FEVER

The very characteristic clinical picture of relapsing fever shows little similarity with typhus fever.

After an almost completely symptomless period of incubation, the duration

¹ *Loc. cit.*, pp. 166 and 167.

² *Spilmann, loc. cit.*, p. 627.

of which varies between five and seven days, but which may be as short as three days, the disease almost invariably begins suddenly with a severe chill. The temperature rises rapidly and inside of a few hours attains very high ranges. But very rarely is this initial chill absent, the rise of temperature being noted by sensations of chilliness. Immediately after the onset of the affection, the subjective sensations of the patients give evidence of the severe affection. Very severe, intense headache appears, marked pains in the lumbar region and in the limbs compel the patient to take to bed, and conspicuously rapidly, even upon the second day of the disease, marked prostration is present. With this, the skin is hot and dry, the axillary temperature very high, frequently above $105\frac{1}{2}^{\circ}$ F. and the pulse greatly excellerated, usually above 120, but with this it is full and strong, often bounding. The patients are tortured by great thirst, the appetite has disappeared completely, the tongue is thickly coated, vomiting is present, the bowels are frequently constipated, but rarely is diarrhea present.

Very characteristic of the disease are the intense muscular pains, which often compel the patient to remain motionless. They are most intense in the muscles of the calves, where slight pressure produces marked sensations of pain, but the upper extremities and the muscles of the trunk are also implicated. I remember a case in which the abdominal muscles were so sensitive to pressure that peritonitis was assumed until the further course of the affection cleared the situation. The respiration, in keeping with the high fever, is very frequent, occasionally the rapidity is excessive without any anatomical lesions of the respiratory organs being present. It is then due to muscular pains of the thoracic and abdominal muscles, which give rise to pain with every respiratory movement.

In the heart there is frequently heard, more often than in other typhoid diseases, systolic murmurs, without an endocarditis being present, which disease presents a very rare complication of the malady.

The spleen enlarges very rapidly and to a marked extent, almost at once a large area of the same is found below the margin of the ribs, so that palpation of this very tense segment does not give rise to difficulty. The spleen is usually sensitive to pressure upon palpation, this painfulness may even arise spontaneously during respiratory movements. The acute swelling of the spleen may occasionally be so great that the capsule ruptures, and the patient succumbs with the symptoms of an internal hemorrhage or a peritonitis.

The liver also enlarges, but to a less extent, and is also sensitive to pressure.

The urine shows the characters of febrile urine, and in many cases contains more or less albumin.

This severe clinical picture lasts for a number of days, usually over a week, the fever remains high, of a subcontinued type, the morning remissions being but slight, and the very rapid pulse gradually becoming smaller and softer. The patient, on account of the muscular pains, does not move, he is apathetic, however, in full retention of his senses; the color of the face, in spite of the high fever, is conspicuously pale, slightly cyanotic and yellowish. The prostration increases from day to day. The sleepless patient, on account of the pains in the head and muscles, emaciates to a great extent. Toward the end of the week, an increase even of these morbid phenomena shows itself. The

temperature rises and in comparison with other diseases, reaches unheard-of heights, the frequency of the pulse is over 140, it is small, frequently intermittent, the cephalalgia is even more severe; the mind which has been clear up to this time begins to be cloudy, the tongue becomes dry, delirium appears. This increase of the symptoms usually ushers in the crisis, which occurs at the end of the first week, causing an abrupt change in the symptoms, being more intense and more rapid than in any other affection which terminates by crisis. With a profuse outbreak of sweat, the temperature falls within a few hours from the highest febrile ranges to the lowest subnormal ones, falls in temperature of 7 and more degrees may occur in this way. The patient who upon the morning has been seen with a hot, glowing skin, burning thirst, galloping pulse, flying respiration, is found in the afternoon bathed in sweat, with an unusually cool skin, slow pulse, and quiet respiration.

As a rule, the differences in the frequency of the pulse are not so great as those of the temperature, but they may also be very marked, as the enormous, frequent pulse before the crisis, as has already been mentioned, may fall during the crisis to subnormal values, and, with this, differences of 80 beats per minute and more may occur. Exceptionally in this rapid defervescence, instead of the critical sweat, or simultaneously with it, other phenomena appear: Profuse vomiting, diarrhea, often showing a hemorrhagic character, other hemorrhages, such as cutaneous hemorrhages, epistaxis, hemorrhages from the genitalia, meningeal hemorrhages, with the phenomena of pachymeningitis hemorrhagica. The occurrence of the latter shows itself in the clinical picture in that the patient who has had a clear mind during the attack, after the appearance of the crisis, becomes somnolent, with increasing coma, usually with the rapid production of a bed-sore or a pulmonary inflammation; the patient succumbs in a few days. Even where these phenomena are absent the condition of the patient during the crisis is by no means good; the loss of power is extreme, vertigo occurs, often severe collapse is noted, and not rarely death occurs during the critical defervescence.

However, after the completed crisis, euphoria is manifest, the tongue clears, appetite returns, and the patient regains strength exceedingly rapidly after this severe disease. Body weight increases, temperature and pulse slowly regain their normal height, enlargement of the spleen and of the liver decreases and the patient feels himself so completely recovered that he looks upon his convalescence as certain. In this stage some patients leave the hospital, and absolutely disregard the warnings of the physician, until, commonly after the course of a week, the relapse occurs. Just as suddenly and as unexpectedly is the reappearance of the disease, the chill occurs and now the same clinical picture repeats itself as in the first attack, only with this difference, that the second attack is almost always of briefer duration; whereas the first attack usually terminates in from six to seven days, the second attack lasts only four to five days and then ends in the same critical manner. For the most part, this definitely terminates the affection. It is true, not rarely—in some epidemics, even very frequently—the second period of apyrexia is followed by a third attack which is again two days shorter, here and there even by a fourth and a fifth, which successively become briefer in duration. Sometimes, on the other hand, even though rarely, the disease exhausts itself in one attack.

Quite the opposite of the attacks is the condition of the intermissions, these constantly becoming longer, whereas the first lasts from six to eight days, the second is from eight to ten days, and the third from ten to twelve days.

There are many deviations from this typical course of the process in relapsing fever. Occasionally, even though seldom, the rise in temperature is less abrupt, sometimes the fever is not so continuous, occasionally the critical defervescence is less marked and rarely the defervescence occurs by lysis. Preceding the true crisis, pseudocrises often occur, which only differ from the true ones in that the defervescence is not permanent. If these pseudocrises increase, the whole or a part of the attack may show an intermittent febrile course. None of these varieties are of special importance and do not greatly modify the clinical picture.

In the description of relapsing fever we have omitted a very important symptom-group, namely the *changes which are shown by the blood of the patient*. During the attack a leukocytosis appears, which increases during the course of the attack up to the time of crisis, and is more marked than in any other infectious disease. The older counts which originated in a period during which the modern aids to blood counting were not known, therefore depend entirely upon estimations. They are certainly too high as are also the older reports regarding the proportion of the red and white blood cells in leukemia. Nevertheless, it is seen from them—in one case the proportion of the white blood cells to the red is estimated as 1:3—that the leukocytosis is enormous. Actual leukocyte counts have only been reported during the last Russian epidemics. According to their results, the number of leukocytes is not so exorbitant. Detailed reports regarding the course of leukocytosis are given by Sawtschenko and Malkich.¹ According to them, the number of leukocytes increases gradually during the attack, reaches its acme before the crisis, and falls during this period; in the first intermission, normal numbers are gradually reached, in the later ones they appear rapidly.

As usual, the leukocytosis is a polynuclear one, the previously mentioned authors, however, assert that the mononuclear leukocytes increase in number but to a less extent, and in the manner that their increase and decrease occurs one to two days after the appearance of the polynuclear leukocytosis. The mononuclear leukocytes are often fatty and vacuolated. Besides them, there are found in the blood vascular endothelia which are also fatty. During the attack it is further shown, as in all other febrile diseases, that there is a diminution in the erythrocytes and in the hemoglobin.

However, the most important change in the blood is the appearance of the *spirilli*. These are delicate cork-screw-like, twisted threads and are in constant motion. The spiral moves up and down, and the body of the spirillum simultaneously moves forward. With the approach of the crisis, the movements become slower, more of a lateral movement being noted, so that the body of the spirillum bends, whereas the windings of the spiral become less distinct and more irregular. Besides this, the spirilli show a great tendency to collect, partly forming long threads, partly giving rise to stellate formations, the centre of which is formed by immotile, baked together spirilli, the

¹ Annales de l'Inst. Pasteur, xv, 1901, Nr. 7.

terminal filaments of which, adhering to the centre, are in more or less active movement.

It is not quite easy to see these fine animate organisms, but I have the impression that this difficulty is exaggerated in the newer publications. Of the epidemic in which I observed the spirilli myself, I have not retained the recollection of such great difficulties, and since the microscope has been so much improved the detection of the spirilli should have become easier. The detection of the spirilli is facilitated by the fact that their movements are communicated to the erythrocytes and may be observed from the red blood corpuscles.

A further improvement, which at that time was not at my command, is the investigation of stained, dry preparations, which, according to Nikiforoff, are best fixed in alcohol and ether. Apart from the simple staining with the usual staining media, which are usually quite sufficient, there are still a number of methods that, by the isolated staining of the spirilli without covering the red blood corpuscles or by means of a contrast staining of these, facilitate the detection of the spirilli.

The number of the spirilli varies greatly. Occasionally they are so few that they are not found in the febrile attacks. A parallelism between the fever and the number of spirilli does not exist. In general they increase from the beginning of the attack, so that, finally, in a field of the microscope, many, up to a dozen and more, are observed, whereas at the onset, in many fields of the microscope, only here and there one could be seen. Shortly before the crisis they disappear but reappear again with the critical sweat. Only exceptionally they are found in the blood during the first days of the intermission. They reappear in the relapse and show the same phases as in the primary attack.

It has already been noted that in this relation between the appearance of the spirilli and the attacks, the importance of the etiological significance of the spirilli has been found very early. However, great difficulties were encountered in giving a satisfactory explanation of the disappearance of the spirilli from the blood during the crisis and their reappearance during the relapse. The explanations which we now have for this phenomenon are still not quite satisfactory. I shall omit the older views which are not consistent with our present knowledge, and shall at once refer to both of those which at present are opposed to each other. The one originated with Metschnikoff who believed that he found the fate of the spirilli in relapsing fever as a classical example of his law of phagocytosis.¹ He examined the various stages of the disease in infected monkeys and found that during the attack the spirilli only circulate in the blood, that immediately before the crisis the spirilli which disappear from the blood enter the spleen, and during the period of apyrexia are gradually taken up by the polynuclear leukocytes and destroyed by them. Finally, the satiated phagocytes are incapable of taking up all of the spirilli, a portion of them remaining free between the cells and forming the starting point for a new generation that produces the relapse. The report of Metschnikoff has been proved to be very theoretical and in individual points has received

¹ *Metschnikoff, Der Phagocytenkampf beim Rückfallstyphus. Virch. Arch., Bd. cix.*

considerable criticism but the most important fact of his investigations, the emigration of the spirilli into the spleen and their being taken up by the cells of the spleen has been generally confirmed. But Metschnikoff's explanation has been combated, the majority of investigators in the realm of immunity do not believe phagocytosis to be an important factor in the battle of the organism against the germs of disease, but only a secondary process for the complete annihilation and carrying away of the already dead microorganisms. So also in relapsing fever, Metschnikoff had from the start guarded himself against this opposition, that during the apyrexia he was able to produce new transference with the spleen containing spirilli, but his hypothesis still left much that was not clear: It did not explain, for example, why the spirilli so suddenly leave the blood and enter the spleen during the crisis, and finally, it was shown that it was impossible for the spleen to exclusively bring about the cure of the disease, as Metschnikoff assumed, for apes in which the spleen was removed were able to recover from an inoculated attack of relapsing fever.¹

The other theory depends upon the immunizing protective bodies which are formed in relapsing fever as well as in other infectious diseases. The acquired immunity in relapsing fever is not very great, numerous observations have shown that reinfection soon after recovery from the disease in man is very frequent, and also in monkeys. In a short time after recovery, a fresh attack may be developed by inoculation. But a certain degree of immunity is nevertheless present which is shown in the fact that in a reinfection in man, as well as in apes, the disease runs a very mild course. This immunity is regarded by Gabritschewsky² as due to bactericidal substances that he has demonstrated in the blood of relapsing fever patients. If there is mixed upon the cover-glass a drop of blood serum containing spirilli, with a drop of serum of a relapsing fever patient during the stage of apyrexia, at a temperature of the room, after two to four hours, at the temperature of the body in from one-half to one hour, the spirilli become immotile, swollen, granular, and are finally destroyed. If, on the other hand, there be mixed in the same manner blood containing spirilli with normal blood serum, the spirilli upon the average retain their normal movements for one hundred and sixty hours. This condition is nothing more than the well known Pfeiffer phenomenon; as in Pfeiffer's case, the cholera spirilli in the peritoneum of the cholera-immune guinea-pig, so in this instance the spirilli of relapsing fever, are dissolved in the blood serum of a relapsing fever patient. The bacteriolytic action of the relapsing fever serum is a specific one, only influencing the spirilli of relapsing fever, and in other respects these substances show all the peculiarities of Pfeiffer's bacteriolytic antibodies.³ They are probably formed during the entire attack in an especially profuse amount, however, particularly before the crisis; during the apyrexia they are gradually excreted, and according to

¹ *Tietin*, Zur Frage über die Bedeutung der Milz bei Febris recurrens. Centralbl. für Bakteriologie, etc., xv, 1894.

² *Gabritschewsky*, Les bases de la sérothérapie de la fièvre récurrente. Annales de l'Institut Pasteur, x, 1896.

³ It is possible, as was proven later, to produce in animals that are refractory in themselves, as in the guinea-pig, bacteriolytic antibodies by a process of active immunization, and then Pfeiffer's experiment may be carried out with relapsing fever spirilli.

Gabritschewsky's reports, especially rapidly immediately before the appearance of the relapse.

Gabritschewsky believes that the sudden disappearance of the spirilli from the blood is due to the appearance of these bacteriolytic substances. As soon as the amount of bacteriolysines in the blood has reached a certain proportion the spirilli are destroyed by solution, completely; a part of them becomes immobile, and by simultaneously appearing agglutinating substances they become adherent to each other. The immobile and agglutinated spirilli are brought to the spleen and destroyed by phagocytosis. The relapses are explained by Gabritschewsky by the assumption of resisting, developing forms of spirilli—spores—which escape the action of the lysines and as soon as the latter are excreted, during the stage of apyrexia, they form the point of origin for a new generation, and with this a new attack occurs; the briefer interval of the attacks and the increased duration of the period of apyrexia, justifies the assumption that in each new attack the lysines are produced in greater amounts and become more resisting, so that finally they are sufficient for the complete annihilation of the spores.

This theory also has many weak points, primarily the assumption of spores. I have previously mentioned, that in former times these were regarded as an explanation of the pathology of relapsing fever, that, however, never in the attack nor during the apyrexia have such durable forms been determined. Metschnikoff¹ called attention to this, and emphasized further, how varying and slight were the bacteriolytic values of the blood which were found by Gabritschewsky.

Gabritschewsky² then improved his theory upon the basis of further study. His observations were no longer made with relapsing fever, in which extensive investigations were difficult to carry on, not only on account of the scarcity of material but also by the exclusive use of valuable experimental animals such as monkeys. He utilized a spirilli-disease of geese, which was discovered in the Caucasus and which showed many analogies to relapsing fever, the micro-organism of which, however, was not identical with that of relapsing fever. In the geese infected by him he found first, the interesting fact, that the spirilli before they appear in the blood increase in the spleen and liver only then entering the blood. Further, he determined that the bacteriolytic property is not the same in the entire body, that it is much less in the spleen than in the rest of the blood; he therefore assumed that the spirilli do not alone enter the spleen but that they are destroyed in the blood, that they are not dissolved in the spleen but only weakened and succumb there to phagocytosis. Those which are spared, form the point of origin for the relapses. The production of bacteriolysines in the goose, as in the human being, goes hand in hand with leukocytosis, and is in connection with it.

But even in this form, the explanations of Gabritschewsky have been contradicted. Sawtschenko and Melkich³ utilized the material of an epidemic prevailing in the winter of 1900 in Kazan for new investigations; the principal observations of Gabritschewsky were confirmed by them, but a number of

¹ *Annales de l'Institut Pasteur*, x, 1896.

² *Gabritschewsky*, Beiträge zur Pathologie und Serotherapie der Spirochäteninfektionen. *Centralbl. f. Bakteriologie*, etc., xxiii, 1898.

³ *Loc. cit.*

new facts were also discovered. Metschnikoff had determined that the bacteriolytic phenomena in the peritoneum of the guinea-pig could be prevented by the development of an artificial leukocytosis; then, in place of Pfeiffer's phenomenon, an active phagocytosis occurred. Both authors confirmed these phenomena regarding the spirilli of relapsing fever, and determined by very ingenious experiments, that under these circumstances the bacteriolytic substances are absorbed by the leukocytes and that the leukocytes which only slowly take up living spirilli acquire the property of a very rapid phagocytosis. The leukocytes which under normal conditions are chemotactically negative to spirilli, by absorption of bacteriolysines, become chemotactically positive. If these results are confirmed they are certainly very interesting, but they do not shed especial light upon the processes in relapsing fever. Further, both investigators have, in a number of patients, taken the temperature daily, amount of leukocytes, bacteriolytic power of the blood serum, and agglutination property, and have determined them quantitatively. With this, they found that in the amount of blood the bacteriolysines rise to very slight values during the attack and during the crisis, they also remain slight during the first period of apyrexia. Only in the second and third stages of apyrexia, and almost always upon the second day after the crisis a great increase in the value occurs, which diminishes rapidly if a new attack is to be expected. On the other hand, in a definite defervescence, after a brief fall, it rises again, remaining permanently high. Sawtschenko and Melkich conclude from this, that the bacteriolysines have nothing to do with the disappearance of the spirilli in the crisis, but that they are only in connection with a definite cure and with immunity. Critical defervescence and disappearance of the spirilli are moreover in connection with the phagocytosis. By the latter, the phagocytes are empowered to take up by absorption the bacteriolytic substances which form in small amounts, which on their part are again products of the activity of the blood phagocytes. I cannot say that I find this theory very satisfactory for, as the authors themselves recognize, it certainly leaves a number of questions unsolved.

The results of all these investigations may, therefore, be looked upon as demonstrating that in relapsing fever leukocytosis as well as the production of bacteriolytic protective bodies, also the conspicuous phagocytic processes in the spleen, even though less pronounced in the leukocytes of the circulating blood, are directly or indirectly combined with the appearance of the crisis and the cure of the disease. It has not been determined up to now in what connection these phenomena stand to one another, and what direct influence they exert upon the symptoms and course of the disease.

Among the symptoms of the disease there must be mentioned further that *herpes labialis* is extremely frequent, having been seen in one-fourth, even in one-third of the cases. The appearance of this eruption is not limited to any distinct period of the disease; it shows itself in the intermission as frequently as during the attack. Other *cutaneous eruptions* are also observed during the course of relapsing fever. Sudamina are quite frequent, and a desquamation which is not very rare is probably in connection with them. Here and there an exanthem occurs that resembles the roseola of enteric fever; other eruptions have also occasionally been observed. The peculiar color of the face has already been mentioned, this having been described as a bronze-color or

lead-gray; severe cases are said to be characterized by a deep purple redness of the face at the onset of the disease. Conspicuously frequent, before the apyrexia is an edema of brief duration which occurs in the lower extremities, without any complication on the part of the kidneys or the heart being present.

As in all infectious diseases, so also in relapsing fever, the disease may vary greatly in regard to its intensity, but I have the impression that the differences are not so extensive as in typhus fever, enteric fever, and in most of the other acute infectious diseases. Especially in the first attack, the morbid phenomena are commonly well developed, and the milder cases are only distinguished in that the temperature and frequency of the pulse does not become so excessive and that the attack does not last so long. The differences of intensity which are due to the number and severity of the relapses are more marked. As already mentioned, here and there, the relapse may be absent entirely (*recurrens sine recurso*, the usual course of inoculated relapsing fever in monkeys). More frequently the first relapse is very mild, scarcely indicated by a brief elevation of temperature, without decided morbid phenomena, with or without very few spirilli.

A *lethal outcome* is mostly the result of complications. Without these, death is principally due to collapse; this may occur in any stage of the disease, but, however, is most frequent during the crisis, when it results in a fatal issue.

PATHOLOGY

The pathological findings are much more characteristic than those of typhus fever. As a regular change there is usually found a very high-graded enlargement of the spleen, the tissue being soft, friable and of a brownish-red color. Besides these diffuse changes, which are principally due to an increased filling of blood and dilatation of the venous trunks, as well as intravenous extravasation of the intravenous trabeculae with red and white corpuscles, there are found focal phenomena of two varieties.

1. Small lymphomatoid proliferations, principally situated in the follicles, which cause whitish-yellow, pin-head size, partly round, partly striated foci, which coalesce, invade the neighboring parts, and are occasionally surrounded by a hemorrhagic base. They consist of accumulation of lymphocytes that gradually show retrogressive changes, their protoplasm is granular and cloudy, the nucleus losing its property of staining (miliary necrosis). In the periphery of the latter, large cells are found (macrophages), which include red blood corpuscles and microphages containing spirilli. In each new attack there form between the old, which are due to previous attacks, new areas of the same kind. A purulent decomposition of the same, which, according to Griesinger, was said to result frequently, appears to be very rare, according to the latest investigations. The spirilli are found principally in these areas if they are present in the spleen at all. They lie partly in, partly between, mononuclear lymphoid cells, principally in those areas in which necrotic cells are intermingled with these; the cells which contain spirilli are frequently themselves necrotic.¹

¹ The reports of authors are still very contradictory in regard to the condition of spirilli in the spleen, the number of investigations is still too small at present.

2. Infarcts varying greatly in size, mostly below the surface, occasionally deeply situated. They are identical with embolic splenic infarcts but, according to the investigations at our disposal, they can hardly be referred to arterial closure, but in the veins of exit, thrombi are constantly found, which are probably in causal relation to these infarcts. Regarding the causes of these thromboses, the views still differ, partly they are referred to compression of the veins by the previously described foci, partly to a swelling, desquamation and fatty degeneration of the vascular endothelium which is found in relapsing fever in the entire blood vessel system being most pronounced, however, in the spleen, and more developed in the veins than in the arteries. The termination of these infarcts is partly by resorption and scar formation, partly puriform softening and dissociated suppuration, finding its way either into the peritoneum or into neighboring organs.

Very commonly, a perisplenitis forms, in connection with these changes, causing adhesions between the spleen and neighboring organs.

Similar alterations to those in the spleen are also shown in the bone marrow, only here diffuse changes prevail. They give rise to a transformation of the fatty tissue of the tubular bones into red marrow, by proliferation of the osseous medullary elements, and filling and dilatation of the vascular spaces. Frequently from the red basement, white striæ and lines are noted, due to a fatty degeneration of the vessels. Besides these diffuse changes, although more rarely, focal processes are present, which are very similar to those described in the spleen and which go through the same retrogressive changes.

It is still questionable whether the changes in the bone marrow are the same as in the spleen. Metschnikoff denies this and maintains that the spirilli enter the spleen exclusively. His assumption, however, requires new verification with the staining methods, that have been improved in the meantime.

The liver is also commonly enlarged; this enlargement depends principally upon a hyperemia which is in connection with a dilatation of the intralobular capillaries, which increases during the attacks and diminishes during the period of apyrexia. Besides cloudy swelling, the liver cells show no changes; it has not yet been determined definitely, in how far an increase of the interlobular connective tissue by round-cell infiltration occurs, this is frequently present and may be regarded as due to the infectious process or to alcoholism which frequently complicates the disease. Now and then, although seldom, similar infarcts to those in the spleen are noted in the liver.

The muscles, in general, show no characteristic changes. Fatty degeneration and increase of the muscle nuclei, and waxy degeneration of the muscles occur, even though more rarely than in the other typhoid diseases. The heart muscle is often conspicuously flaccid, friable, and fatty.

At the autopsy, in the blood of patients dying during an attack of relapsing fever, the spirilli have been demonstrated after overcoming some difficulties; their presence was already certain before this proof from the very frequent infections which arise from autopsies in which an injury has taken place.

The other anatomical changes will be mentioned in describing the *complications*. Of these two are especially frequent and important.

First, *the pulmonary inflammations*. I refer particularly to the fibrinous inflammation of the lungs, which is a very dangerous complication of relapsing

fever, it occurs very much more frequently in the period of apyrexia, and naturally changes the fever course of relapsing fever to a marked degree. Beginning usually with a chill, in the majority of cases it is fatal; in the cases which run a favorable course, the termination is by crisis if it occurs during the apyrexia. The fever type is still more altered if the pneumonia sets in during the course of the attack. In the sputum which is usually typically pneumonic, the rusty sputum, spirilli have been demonstrated. This pneumonia of relapsing fever differs in no way anatomically from the ordinary form; bacteriologic investigations are not at hand, but it may be assumed, in fact, that they are due to a mixed infection with pneumococci.

Less frequent are bronchopneumonias, which are connected with the catarrhal process of the respiratory mucous membrane which is not so frequent in relapsing fever as in the other typhoid diseases.

Pleurisies, serous and hemorrhagic, have also here and there been observed, empyema is always in connection with a purulent splenic infarct.

The other important complication is *jaundice*. This occurs more frequently in relapsing fever than in other acute infectious diseases excepting yellow fever. The frequency varies in different epidemics, those having been observed in which the number of cases showing jaundice amounted to 40 per cent., whereas in other epidemics this complication was only noted in 3 per cent. The intensity of jaundice, and especially its effect upon the general condition also varies in different epidemics. Occasionally it is without any influence upon the course of the disease. In these cases jaundice appears about the middle of the first attack, increases in intensity, and disappears gradually in the interval, as a rule, without reappearing in the relapse. The latter condition, however, also sometimes occurs, and also the first attack may arise without jaundice, the second attack showing it in its course. The degree of the icteric discoloration may be very insignificant, but may also become relatively intense. Besides discoloration of the skin, bilirubinuria, slowing of the pulse, and itching of the skin have been observed. The stools are occasionally entirely decolorized, sometimes containing bile, and occasionally there is bile-tinged vomiting. The course of the disease, its crisis, the apyrexia, and the relapses are not influenced by this complication. In the first epidemic that I observed most of the cases with jaundice showed this character.

In other epidemics—and this appears to be the more frequent condition—jaundice, on the other hand, is a very serious complication, which gives rise to the severest septic and cholemic phenomena. The symptoms are very severe from the onset, the cephalalgia can scarcely be endured, the conjunctivae are injected, the mind somewhat influenced, the tongue dry and fissured; severe vomiting is present, diarrhea often showing a dysenteric character, and nephritic symptoms setting in. After the appearance of the jaundice, at about the fourth to the sixth day, the apathy and prostration increase, and delirium and somnolence appear. Critical defervescence does not occur, at most a slight, rapidly passing remission in the fever is noted. With a complete development of the typhoid symptom-complex the patient perishes, frequently after a pneumonia has been superadded or hemorrhages of all kinds, cutaneous as well as mucous membrane hemorrhages, have complicated the clinical picture. If the disease terminates in recovery, the disappearance of these symptoms is very

slow, and convalescence is very protracted. At the autopsy of such cases, there are found, besides the previously described changes of relapsing fever, the phenomena of jaundice. The liver is still more swollen, icteric, the enlarged biliary passages are patulous, in the small bile channels swelling and cloudy granulation of the epithelium are noted. Besides these, there are found necrotic processes of the mucous membrane of the pharynx and intestine, ulcers of the larynx, with perichondrial lesions, inflammations of the lungs, pulmonary gangrene, nephritis, in brief, changes similar to those found in autopsies from typhus fever cases.

The name of *bilious typhoid* has been given to these severe cases of icterus, and their connection with relapsing fever was disputed for a long time. Griesinger, who had observed these cases in Egypt, gave the disease this name and designated the cases as relapsing fever occurring simultaneously with jaundice; but this was greatly disputed. The decision appeared to be easy as soon as a certain method of recognizing the spirilli of relapsing fever was attained.

In fact, spirilli have been demonstrated in these cases, and the test by inoculation of the blood of these cases has proven positive. Moczutkowski did not hesitate to inoculate human beings with the blood of such cases, and in this manner produced the usual form of relapsing fever without jaundice. With this there can be no doubt of the similarity of these affections with relapsing fever, and yet the case is not so plain.

Doubt has arisen whether the cases observed by Griesinger in Cairo, and described by him as bilious typhoid, were really cases of relapsing fever. Kartulis¹ has described a disease which has existed endemically in Egypt, and especially in Alexandria for twenty years and which he identified with the bilious typhoid of Griesinger; in this disease, spirilli could never be demonstrated in the blood; unquestionably it is identical with typhus icterodes, an endemic disease of Smyrna, of which Griesinger already assumed that it was identical with his bilious typhoid. The spirilli of relapsing fever are also absent in this disease, as Diamantopulos² has demonstrated. Both diseases have, in fact, great similarity, both symptomatologically and epidemiologically, with the bilious typhoid of Griesinger. They differ from relapsing fever also in that there are no facts which favor their contagiousness. This is also emphasized by Griesinger regarding his bilious typhoids: "Regarding the question of contagiousness, I must expressly declare that in my circle of observation no single fact arose which in the slightest degree favored contagion; the patients were never isolated in the hospital, no other patients in the wards in which they were lying, none of the nurses, none of the students, none of the physicians, who examined the patients daily without taking precautions and who held autopsies upon the cadavers, showed the faintest sign of the disease."³ With all this, some weighty differences may be noted, to which Kartulis has called attention. The disease described by him is unknown in Cairo where Griesinger made his observations, it exists in Alexandria, as also in Smyrna, where typhus icterodes occur during high summer, whereas

¹ Deutsche med. Wochenschr., 1888, Nr. 14.

² Diamantopulos, Ueber den Typhus icterodes von Smyrna. Wien und Leipzig, 1888.

³ Griesinger, Gesammelte Abhandlungen, ii, p. 551.

Griesinger observed the greatest number of his cases in spring and in early summer. The most important among the anatomical differences is that the changes in the spleen, which Griesinger described, are absent in the patients of Kartulis, and also in those affected by typhus icterodes. But the description of the spleen which Griesinger gives, corresponds completely to the findings in the spleen in relapsing fever, and we must arrive at the conclusion that they are due to cases of relapsing fever with jaundice. The intuitive acuity of Griesinger, in which he recognized the cases which varied so greatly from relapsing fever as belonging to this affection, is remarkable. Naturally, it remains questionable whether all cases which Griesinger has counted as bilious typhoid have been cases of relapsing fever. In my opinion it would be best to drop the name bilious typhoid altogether, to designate the cases represented by spirilli as cases of relapsing fever with jaundice, but to count the cases of Kartulis as typhus icterodes. With this, it must be made doubtful how many of the observations of Griesinger belong to the latter disease.

Further, a frequent complication of relapsing fever is the *renal inflammation*. Slight damage of the renal substance and mild albuminuria, due to this cause, with a few hyaline casts, and renal epithelia, are quite without importance. Albuminuria occurs in the course of the attack and disappears after profuse diuresis in the period of intermission. More rarely, but nevertheless, in quite a large percentage of the cases, a severe nephritis, frequently of a hemorrhagic character, occurs. In the latter cases spirilli have been found in the hemorrhagic urine. The nephritic disturbances improve during the intermission, without disappearing completely, to become exacerbated in the relapse. The complication is a very serious one, now and then patients succumb showing uremic phenomena. More or less marked dropsy has also been observed in the nephritis of relapsing fever. The anatomical examination of the enlarged and pale kidney shows changes in the glomerular and of the capsular epithelium, as well as cloudy swelling of the epithelia of the convoluted tubules. If the cases terminate in recovery, the nephritic symptoms improve only provided the acute nephritis was not the recrudescence of a previously existing chronic one.

Very often an *intestinal catarrh* with diarrheic discharges exists during the disease; in severe cases it is not infrequently hemorrhagic and mucoid in character. In a lethal termination the previously mentioned necrotic changes of the intestinal mucous membrane are found. This is not a complication with true dysentery. In general, complications of relapsing fever with other infectious diseases are very unusual. It has been much maintained that, not rarely, relapsing fever and remittent fever occur simultaneously in the same patient. It appears very questionable to me that these cases were true malaria. In any of them this assumption requires proof by the investigation of the blood of such cases for malarial parasites.

Mixed infections with pyogenic organisms are not so common in relapsing fever as in the other typhoid diseases; especially are abscesses, furunculoses and bed-sores much less frequent. I have already spoken of splenic abscesses, which by rupture may give rise to purulent splenitis or left-sided pleurisy; now and then renal abscesses have been observed at the autopsy.

Purulent parotitis and purulent otitis media are not rare, also pyemic

general infection, with puriform, decomposing venous thrombosis, have been observed. None of these suppurative processes have been examined bacteriologically.

A rare, but very characteristic complication of relapsing fever is a *phlegmonous inflammation of the tongue*, with a high degree of painful swelling of the same, and fever which occurs during the intermission; usually its termination has been fatal; in the cases that have recovered, nothing has been reported of a discharge of pus.

Also, in the intermission, in some epidemics, quite frequently *febrile, multiple, arthritic enlargements* have been observed which had the characteristics of rheumatism and improved after a short time by the use of the salicylates. Among the sequels of relapsing fever, the most frequent is an irido-choroiditis, usually of a serous nature. By producing opacity of the lens, it leads to disturbances of sight and gives rise to severe pain but usually heals completely.

Neuritic affections partly in connection with paralysis, partly going hand in hand with severe pains, have been observed as sequels in some epidemics. Not rarely benign phlebitis has been observed after the disease has run its course.

Whereas in other typhoid diseases, especially in typhus fever, pregnancy is not usually interfered with, relapsing fever almost regularly leads to an interruption of the same. This interruption always occurs during the attack, most usually during the first attack. The cause of this is most probably the death of the fetus from infection by the spirilli of relapsing fever. The latter have been repeatedly found in the blood of the fetus.

DIAGNOSIS OF TYPHUS FEVER

On account of the contagiousness of typhus fever, an early diagnosis is of extraordinary importance, but this may be exceedingly difficult. In the prodromal stage, the recognition of the disease is hardly possible, as the initial symptoms are not characteristic enough, by far not as characteristic as in measles, scarlatina, variola, etc. Only in an existing epidemic will the prodromal stage of the disease be recognized with a certain degree of probability, especially if the possibility of contagion allows us to draw conclusions regarding the nature of the disease.

Regarding the first cases, only the appearance of the eruption allows us to recognize the disease; as in all other acute exanthemata, so also in typhus fever, of all the symptoms the eruption is the only one which characterizes the disease; but not as characteristic as in the case of measles, scarlatina, or variola. It is by no means a positive sign for the diagnosis, and frequently gives rise to difficulties. Apart from the fact that the exanthem is more frequently absent than in the previously mentioned diseases, even in those cases in which it exists, its recognition is not always easy; upon its appearance it is usually very pale, and particularly in the first cases, in which the skin is markedly implicated, it is scarcely noticeable. In such cases it is said to be possible to make the eruption more distinct by hot baths.

But even in those cases in which the eruption is visible, its recognition is by no means always easy. It is characteristic where it is well developed; it can always be easily differentiated from measles on account of the pallor and the less marked implication of the face, from enteric fever by the manner in which it arises, its great profusion, the amount of the eruption upon the extremities, and the petechial transformation. But, in spite of all this, the decision in individual cases is not always easy and, as a matter of fact, the differentiation between typhus fever and enteric fever has always given rise to great difficulty among physicians.

The difficulty of differentiation in the later stages is also great. A comatose typhus fever patient, with an eruption but little characteristic and scarcely noticeable, looks very much like a severe case of enteric fever and, in fact, formerly the differential diagnosis depended principally upon this point. I say formerly, for just this differentiation has now become easy, since we possess in the Widal reaction a means which but rarely fails us in the recognition of enteric fever. The differentiation of typhus fever from severe pyemic affection, from malignant pneumonias, from inflammations of the meninges of the brain, may give rise to insurmountable difficulties.

It would lead us too far to describe the points of support to which we must adhere in arriving at a decision. I should have to describe the symptom-picture of all of these diseases. The older physicians laid great stress upon the specific typhus fever odor in the recognition of the disease, but of this it is now maintained that it is not specific and that its existence is doubtful in patients that are kept clean.

DIAGNOSIS OF RELAPSING FEVER

We stand upon a much more certain basis in the recognition of relapsing fever in all instances in which an etiological diagnosis is possible. The proof of spirilli in the blood during an attack is decisive. Naturally, so long as the epidemic is not expected, the examination of the blood is easily omitted. This is scarcely to be feared in hospitals, in which now every severe infectious disease requires the examination of the blood, but this may easily occur in the treatment of patients in private practice.

For this reason the other view points in the recognition of an infection of relapsing fever shall be mentioned again: The very severe febrile phenomena, the marked pains in the head and muscles, the rapidly developing enlargement of the spleen which reaches a high grade. Further, the peculiar bronzing or leaden appearance of the face is designated as characteristic.

It is more difficult if we are forced to make the diagnosis in the period of apyrexia; the history does not always give a sufficiently certain foundation. Here Löwenthal¹ has advised employing Gabritschewsky's test in the diagnosis, to determine the bacteriolytic action of the blood serum upon the spirilli of relapsing fever. This test has already been described by me in Gabritschewsky's experiment. For the utilization of the method, it is

¹ Deutsche med. Wochenschrift, 1897, Nr. 35.

necessary that there be at hand a patient with an attack, having spirilli in his blood. Therefore, this test cannot be utilized in settling the question in the first cases of an epidemic. According to Löventhal's report, the results are satisfactory.

Löventhal has utilized the results of Gabritschewsky's test for another purpose, namely for the definite recognition of the cure of the disease, the satisfactory solution of which was not possible up to now. The patient should only be allowed to leave the hospital when there is no longer danger of a relapse. We will best fulfil this obligation if we compel patients to remain in the hospital fourteen days after the last crisis. But the patients often recover so rapidly that they do not believe in the danger of a relapse and plead to be discharged. In this combat between physician and patient, the physician sometimes does, or must, yield, and then after a short period the discharged patient again enters the hospital; or it may occur that the physician has assured the patient that he will have a relapse, and he has therefore remained in the hospital and later becomes demented.

This has given rise to the attempt to predict the attacks with great certainty. Löventhal¹ believes he has found a solution of this problem in the bacteriolytic blood serum during the period of apyrexia. I have already mentioned that in the intermission this power gradually, and especially rapidly before the appearance of the relapse, is diminished, whereas it was retained for a long time after the last attack. I do not wish to mention the individual prognostic rules of Löventhal, the most important is, that if, after the seventh day of apyrexia, the bactericidal action of the blood serum occurs after an hour, this definitely announces a positive recovery.

PROGNOSIS OF TYPHUS FEVER

The usual outcome of typhus fever, as also that of relapsing fever, is recovery. The mortality in the two diseases, however, is a very different one. The prognosis of typhus fever is much more unfavorable than that of relapsing fever.

The percentage of the fatal cases varies greatly in different epidemics; I have already mentioned that there are epidemics showing particularly mild cases, in which the mortality is proportionately very low. Still it shows 8 per cent. among the most favorable epidemics, as we may note, from older reports, which, however, are suspicious because they originated in times in which the various forms of typhus affections were not yet sufficiently differentiated. On the other hand, epidemics are not rare in which one-half of those attacked die. The causes of these differences are partly due to conditions which are still not understood, partly the mortality is influenced by external conditions, and especially unfavorable are those epidemics arising during times of war and famine. The average mortality has been calculated at about 20 per cent. Very marked differences can further be noted if the mortalities of different ages are considered separately. Youthful individuals are less endangered than older persons; apart from

¹ Deutsche med. Wochenschrift, 1897, Nr. 38.

the first years of life, in which the mortality is quite high, up to the twentieth year of life about 5 per cent. of those attacked succumb to the disease, from the fiftieth year of life, over 5 per cent. Further, of great importance for the diagnosis is the condition of nutrition of the affected individual.

Regarding the points of support which the individual symptoms afford us in determining the prognosis of the particular case, it must first be emphasized, that typhus fever differs from the actual acute exanthemata in that the intensity of the eruption and the severity of the affection do not run parallel. The height of the temperature is not in itself an unfavorable prognostic sign, especially in the precritical rise, temperatures of 107° F. are noted in cases running a favorable course. A very high pulse rate in the early stages of the disease is unfavorable, and especially unfavorable are signs of cardiac weakness, and a small intermittent pulse, and particularly well-marked cyanosis. On the other hand, severe cerebral phenomena in typhus fever are signs of unfavorable prognostic import. Most of the complications, such as pneumonia, nephritis, and parotitis, as well as the gangrenous affections, which almost invariably run a fatal course, influence the prognosis unfavorably.

PROGNOSIS OF RELAPSING FEVER

The mortality in relapsing fever is much less than that in typhus. The mortality varies greatly within wide limits in different epidemics, but a higher mortality than 12 per cent. has not been communicated, whereas, on the other hand, there are smaller epidemics without a fatal case, and larger ones have been described with a mortality of 1 per cent. Of importance for the prognosis is also the age of the individual, youthful persons are less endangered, and from the fiftieth year on, the prognosis becomes quite unfavorable.

Death is due either to collapse, especially during the crisis, or to complications. From this it can be seen that particular phenomena of the disease influence the prognosis in the individual case. The height of the temperature is without importance, as is also the frequency of the pulse during the attack: Temperatures of more than 107° F., and pulse frequencies of 140, which in all other infectious diseases would indicate a fatal termination, do not have this serious import in relapsing fever. On the other hand, during the crisis, the appearance of which in other diseases which terminate critically removes all anxiety, we must be guarded in our prognosis in a case of relapsing fever. A fall below 93.5° F. in the temperature is always serious. But patients even recover after having reached these low temperature ranges.

Hemorrhages during the crisis are always serious, particularly the meningeal hemorrhages, the clinical picture of which has been described previously, almost always terminate fatally.

Most fatal cases are due to complications; pneumonia, nephritis, purulent inflammations are the most frequent causes of death. Of jaundice, we have already mentioned how varying its prognostic import may be in

different epidemics. Those cases designated by the name bilious typhoid, being cases of malignant relapsing fever with jaundice, albuminuria, hemorrhagic diathesis, have a very unfavorable prognosis.

PROPHYLAXIS AND THERAPY OF TYPHUS FEVER

In such a severe affection as typhus fever, in which, as we shall see, the treatment influences the condition but very slightly, prophylaxis must play an important rôle. We have seen the great importance of social unhygienic conditions of all kinds in favoring the production of epidemics. The prevention and removal of these will therefore be an important means of prophylaxis. The power which is given to physicians by our laws will scarcely permit them to attain the position of exerting a decided influence upon this kind of prophylaxis, and we cannot enter into the discussion of all the ways and means which come into question, as we do not desire to enter upon the realm of the social, political, and economic problems.

Regarding the prevention of the importation of epidemics from country to country, from place to place, land quarantine at present bears a well merited discredit. This means has shown itself as very ineffectual, even as harmful, in other epidemic diseases, in that it increases the difficulty of the actual carrying out of effective measures. This is not different in the case of typhus fever. No difficulties should be put in the way of personal communication, but it should be carefully guarded, especial importance being given by physicians to the observation of lodging places of vagrants, and in fact all lodging houses of inferior quality for travellers; also regarding the transportation of clothing, linens, rags, etc., from infected districts, these being disinfected before they are taken from such places. These measures are rendered very difficult by the fact that we rarely learn of the existence of typhus fever epidemics upon our borders. The existence of great pests such as cholera, cannot be disguised for a long time, whereas typhus fever, the spread of which is limited, does not have general attention drawn to it to the same degree. It frequently occurs that I note in neighboring States, on the other side of our eastern borders, typhus fever epidemics of which nothing is known upon our side of the boundary. If the importation has occurred, the hindrance and distribution, even the early diagnosis, and the most careful isolation of the suspected individual, with disinfection of his effects, of the dwellings and rooms in which the disease has taken place, the isolation of all of those that have been exposed to contagion and the disinfection of their effects must at once be resorted to. We saw in this city a few years ago that in this manner it is possible to limit the distribution of the disease, and to prevent the development of an epidemic.

Even in an existing epidemic these preventive measures, in a somewhat modified sense, are to be employed in limiting the distribution of the disease. Individual views are still too strong at the present time to compel each case to be treated in the hospital, but this course should be strictly adhered to in every case in which complete isolation, and especially a thorough disinfection of all belongings of the patient, is impossible. The

family, in so far as they are not necessary in the nursing of the patient, are to be kept away from the sick, and must be quarantined from the outside world for at least two weeks.

To prevent the spread in hospitals, even there a strict isolation must be carried out. Most valuable in larger epidemics is the erection of improvised typhus fever hospitals, which, of course, dare not take in the different typhoid affections, such as cases of relapsing fever and enteric fever which often occur simultaneously during the same epidemic. Only those cases of which the diagnosis is absolutely certain should be placed in these typhus fever hospitals. On the other hand, to make it possible to isolate the patients, even in the early stages, divisions are to be instituted in the hospital, in which doubtful cases are to be admitted. As soon as the diagnosis of typhus fever has become certain the patients are taken from there and placed in the typhus fever division, those in whom it is shown that typhus fever is not present must be kept in a quarantine division fourteen days longer.

To prevent danger of infection among the physicians and nurses, only immunes are to be employed in these departments. In countries in which typhus fever is endemic this can be accomplished without difficulty, in other countries it would be impossible. I have already called attention to the fact that contagion is especially liable to occur in impure air, it has also been shown that the better the sick-room is ventilated, the less the danger of infection. In summer the patients are best treated in the open air, in winter with the windows open, the low temperature of the surrounding air not only does not injure the patient but even favorably influences his condition. Eight years ago, in a circumscribed epidemic managed in this manner, there was no contagion among the nurses and physicians in our hospital, although the hygienic conditions were by no means of the best.

PROPHYLAXIS OF RELAPSING FEVER

In the prophylaxis of relapsing fever the same measures which have been described for typhus fever are indicated. With the slower spread from case to case, the distribution of the disease can be easily checked by an early recognition of the affection. With respect to the importance which vermin of all kinds have in the distribution of the disease, the disinfection of beds, clothes, linen, etc., will play an especially important rôle. It is even possible that in a very careful disinfection of the effects, in a clean hospital, the danger of transmission may be diminished to almost nothing, so that isolation of patients under these conditions appears to be superfluous. In fact, formerly, although a sufficient disinfection was not then possible, the relapsing fever cases were often not isolated; as an assistant physician, I had to act under these conditions without hospital infection being particularly frequent and compelling us to abandon this system. In a second epidemic contagion was, however, much more frequent and I would not now regard it as wise not to isolate the patients, even if it were definitely proven that the transmission of relapsing fever only occurs by parasites, as the complete annihilation of these vermin, especially of fleas, cannot be counted upon with certainty in all cases.

TREATMENT OF TYPHUS FEVER AND RELAPSING FEVER

But little that is positive can be said of the actual treatment of typhus fever. It is generally admitted to-day that it is not possible, with the means and remedies at our command, to actively influence the course of typhus fever, to bring about the crisis, or to abort the disease. Between the period during which illusions were maintained in this respect and the present time, a long period of resignation has existed. Nowadays some results have been attained in analogous affections, so that this object is looked upon somewhat more hopefully, but in typhus fever, at present, there are no points of support which might indicate a specific treatment. The case is different in relapsing fever, here again it was Gabritschewsky¹ who, upon the basis of his discovery of the bacteriolytic properties of the blood serum of relapsing fever patients and upon the basis of the connection in which he regarded these properties with the cure of the disease, proposed to attempt a specific mode of treatment. He first showed that in animals also that are refractory to inoculation of relapsing fever, spirilli bacteriolytic bodies could be detected in the blood serum after subcutaneous and intravenous injection of blood containing spirilli. After repeated injections of this kind in horses, which were followed by a febrile reaction without the appearance of spirilli in the blood, he obtained a blood serum having quite high bacteriolytic values. He made a sero-therapeutic test in an infected monkey and, in fact, the course of the affection in this case appeared to be favorably influenced. One year later Löwenthal² communicated the results of extensive tests in human beings. The prevention of the relapse, while the bacteriolytic power declined during the pyrexia, was to be prevented by injection of the serum into the blood, and for this purpose the serum of horses, which were prepared in the previously described manner, after the third day of apyrexia was injected two to three times. The amount injected was not always the same, as the serum of the horses at his disposal showed a varying bacteriolytic action. Of those so treated, one died, certainly, however, not as the result of treatment. On the other hand, the well-known consequences of the injection of serum which occur in the treatment of diphtheria—febrile eruptions, arthritic inflammations, albuminuria—were quite frequently observed. The result was, in fact, very conspicuous, 47 per cent. of those treated showed no relapse, whereas the highest percentage of relapsing fever sine recursu observed up to that time amounted to 25 per cent. That these results did not depend upon the peculiarity of the epidemic is shown by comparison with those not treated in this manner, in which only 12.8 per cent. escaped the relapse. At all events, this is a very remarkable result, which of course requires further investigations. Should these prove favorable, it will undoubtedly seem to afford a method of obtaining a high-grade serum, and to build up the estimation of its value so that the process may become practical. Apart from this still insufficiently developed and uncertain method of treatment in the case of relapsing fever as well as in typhus fever, the treatment is purely symptomatic and dietetic. Regarding the former affection, in such a severe febrile disease there must be primarily considered the question

¹ *Loc. cit.*² *Deutsche med. Wochenschr.*, 1898, Nr. 43 u. 44.

of reduction of temperature. The value of drug antipyretics is very slight at present, and antifebrile measures will only be employed here and there, and then less with the object of reducing the temperature, than to quiet very irritable patients. More valuable in the treatment are agents which withdraw heat, especially cold baths. The older physicians among us that have had the opportunity of noting how greatly the results in the treatment of enteric fever have been improved by the introduction of hydrotherapy, will with difficulty be convinced that all this was only a matter of personal delusion. It is true, in the case of typhus fever, cold baths act less obviously than in the case of enteric fever. The only large epidemic of typhus fever that I had an opportunity of seeing occurred during the period when we were sanguine over the new method of treatment of enteric fever, and I still remember the disappointment which this method gave rise to in its application in typhus fever. This was partly due to the fact that we could not succeed in reducing the continuous temperature of typhus fever by the withdrawal of heat, and even the cerebral phenomena were much less reduced than in the case of enteric fever.

In other epidemics this appears to have been different and, for this reason, it will still be well not to abandon this method of treatment. Naturally, the baths are to be used moderately cold—68° F.—77° F., not in a forced manner—sufficient rest should be given the patient between the baths and these should be given at a higher temperature if their application does not bring about a quieting influence upon the nervous phenomena. Apart from the action, which is usually attributed to the baths, they present such great advantages to the patient by the beneficial effect on the skin and the prevention of bed-sores, and by bringing about deeper inspirations and the prevention of atelectasis, that for these reasons alone they should not be omitted. In their use, however, the condition of the heart must always be regarded. In cases of threatening collapse due to cardiac asthenia they should be omitted.

Among the hydropathic procedures belong also cold affusions, which are used as a valuable method of stimulation in conditions of deep depression of the cerebral functions. I must admit that the older I become the less I employ this method, as I have never seen greater effect from it than a very rapid, transitory flaring up of the powers of life. Very grateful to the patient and for this reason advisable, on the other hand, is the permanent cooling of the head by an ice-bag or similar apparatus, this at least diminishes the very tormenting headache.

The second important indication is the treatment of the cardiac weakness which becomes more and more pronounced during the second week; this requires the use of stimulants. The permanent employment of alcohol is now generally omitted, as being valueless. Alcohol is only permanently given if the patients are accustomed to its use and, naturally, at present this is the case with the majority of all typhus fever patients. Alcohol, however, is a very valuable stimulant and, as such, is in general use in cardiac asthenia and threatening collapse; other stimulants next to it in value are camphor, musk, caffeine, etc. If in such conditions, the body temperature falls, the application of external heat by the use of hot bottles, etc., is indicated.

In *relapsing fever* the employment of antipyretic methods is still less indicated; quite apart from the fact that the febrile temperature can only

be influenced with difficulty, the febrile epoch is brief, its influence upon the cerebral functions is much less developed and is more rapid and transitory. The important point of the symptomatic treatment is the guarding of the crisis and the threatening collapse which occurs during this period. The low ranges reached by the temperature during the crisis are combated by the application of heat, warm drinks, and stimulants, the dose being according to the indication.

It would be a great gain if it were possible to combat the danger which is caused by the complication of relapsing fever with jaundice. Unfortunately this is not possible. Griesinger believed he had found an active remedy in quinin, although in fact this has not proven to be the case. On the other hand, calomel recommended for this purpose has also been found to be without influence. We are compelled, therefore, to adopt a treatment which recommends itself to the requirements; we must do what we can, but this, unfortunately, is very, very little. Regarding the dietetic hygienic treatment, not much can be said. In typhus fever, care must be taken in placing the patient in bed, in moving him about from time to time, also the most scrupulous care must be observed in keeping the bed and the body of the patient clean, in order to prevent bed-sores. In relapsing fever, these only arise in the very severe complicated cases.

In regard to diet, in cases in which disease of the intestinal canal is absent, we need not be as strict as in the case of enteric fever; the nourishment should be fluid during the time of fever as the patients reject solid food. If this is not the case, small amounts of pappy and solid food, rice, grits, even some meat may be allowed. It will serve a useful purpose to give the patients large quantities of fluid, not only to satisfy the requirements of the semicomatose patients, but to see to it that, regularly, quantities of fluid are administered to him without his request. This copious flooding of the body, which has shown itself as valuable in enteric fever, is also of value in typhus fever and relapsing fever. Apart from other more theoretical view-points—the increased excretion of toxins—which may even be questionable, the copious flooding of the body certainly favorably influences the renal functions. After defervescence when the appetite of the patient begins to return, the desire for food may be satisfied without fear, and even after a very brief period, normal, nourishing food may be allowed.

DENGUE

By J. C. WILSON, PHILADELPHIA

Definition.—An acute infectious disease of tropical and subtropical climates, characterized by a febrile paroxysm with recurrence, intense pains in the joints and muscles and an early erythematous and a late polymorphous eruption.

“This disease, when it first appeared in the British West India Islands, was called the *dandy fever*, from the stiffness and constraint which it gave to the limbs and body. The Spaniards of the neighboring islands mistook the term for their word DENGUE, denoting prudery, which might also well express stiffness, and hence the term DENGUE became at last the name of the disease.”

The popular term *break-bone fever* denotes the atrocious character of the pain.

Etiology.—Dengue first excited general attention by its epidemic prevalence in the West India Islands in 1827. David Brylon had described in 1779, under the name of *Knockel Koorts*, an epidemic disease which prevailed among the natives and colonists of Batavia. Benjamin Rush observed a similar outbreak in Philadelphia in 1730. His description is one of the first and best accounts of the disease. The disease was then as now known in North America as break-bone fever. Between 1826 and 1828 it prevailed widely in the Southern States and along the Gulf coast. Dickson's account of that outbreak as it prevailed in Charleston is most graphic. He states that in many instances all the members of large households were attacked without a single exception. Since that time there have been many epidemics in Eastern countries while in America there have been five or six widespread outbreaks in the Gulf States and along the Atlantic seaboard as far north as Virginia.

Dengue is in the strictest sense a pandemic disease. No other disease, with the exception of influenza, has prevailed so widely and attacked so large a proportion of the population. Not less remarkable is its rapidity of diffusion. In Galveston in the epidemic of 1897, 20,000 persons were attacked in the course of two months. Dengue is a disease of warm climates and of warm seasons. When it has recurred in the summer in temperate climates it has disappeared upon the appearance of frost.

All races are alike liable to it. Neither age, sex, nor occupation confers immunity. It prevails chiefly in the cities, less generally in the open country. To this statement, however, there have been notable exceptions.

A *micrococcus* has been found in the blood by Dr. McLaughlin of Texas. The period of incubation has been given as from three to five days. At the

beginning and at the height of epidemics it has not in some cases exceeded a few hours.

Symptoms.—The invasion is abrupt. Prodromes are unusual; when present they consist of lassitude, headache, a furred tongue, loss of appetite, muscular soreness, and chilliness.

The attack begins with intense headache, backache and severe pains in the joints and muscles. The affected joints become swollen, and the face and neck are flushed and turgid. Movements are executed with pain and difficulty. Conjunctivitis, swelling of the eyelids, intolerance of light, and stiffness of the muscles of the eyeballs are frequent. The tongue is heavily coated, and epigastric distress is followed by nausea and vomiting. Appetite is lost, and the bowels are constipated. Thirst is not urgent. The temperature rises rapidly, often reaching by the end of the first twenty-four hours 106.7° to 107.6° F. (41.5° to 42° C.).

The pulse is tense and frequent, 120 to 140. The breathing is quickened, the skin hot and dry. Confusion of thought and delirium occur, and in children the attack may begin with convulsions. An erythematous rash appears in many of the cases.

The duration of the first febrile paroxysm is variable, lasting from a few hours to several days, the average being about three days. The defervescence is commonly sudden, often with the occurrence of critical discharges, such as profuse sweating, epistaxis or diarrhea. The eruption now disappears; the skin becomes moist and there is an amelioration of the pains in the muscles and joints.

The period of apyrexia lasts two or three days. In some cases it is wanting altogether, or so brief as to be overlooked. There are cases in which the fever falls but does not quite reach the normal. Notwithstanding the great relief which the patient experiences, there remains some headache and stiffness of the muscles and joints. At the expiration of several hours, more commonly of two or three days, the second febrile paroxysm sets in. The symptoms are much the same as those of the initial paroxysm but less intense. An eruption of variable character develops at this stage of the disease. It is sometimes macular like the rash of measles, or diffuse and erythematous like that of scarlet fever, or papular. Sometimes it is like an urticaria, and there are cases in which vesicles occur. Appearing in many instances, first upon the hands and feet, this eruption generally invades the greater part of the surface of the body. In other cases it is restricted to certain areas. It is attended by distressing itching, and gradually fades after two or three days, being followed by a furfuraceous desquamation. The duration of the second paroxysm is from two to three days. The fever subsides by lysis; the acute symptoms disappear and the patient enters upon convalescence much enfeebled, the muscular pains and stiffness of the joints often persisting for a considerable time. The small and large joints are alike involved, many being affected at the same time or in rapid succession. The muscles are also stiff and sore, and this with the turgid condition of the integuments greatly increases the difficulty and awkwardness of movement, especially in the fingers and hands. In severe cases the mucous membrane of the mouth, throat, and nose is inflamed. The secretion of saliva is sometimes increased and the salivary glands and in

particular the parotid, are swollen and tender. The superficial lymphatics about the angle of the jaw and in the groin are in some cases enlarged.

The urine during the access of fever is scanty and of high color. With the crisis the quantity is increased. Albuminuria is not usually present.

Dengue is seldom fatal. Dickson saw three deaths in the epidemic in Charleston in 1828. Porcher in the epidemic of 1880 in the same city could not learn of a single death.

The diagnosis is not difficult. No other disease spreads with such rapidity through a community and attacks so large a proportion of the inhabitants. Influenza, which resembles it in its epidemic prevalence, differs wholly in its symptoms. From acute articular rheumatism it differs in its course and duration as well as in the eruptions which attend it; from scarlet fever and measles, in everything except the occurrence of the rashes, which resemble the exanthems of these diseases only in the most superficial way; from relapsing fever in all things except its course, and from yellow fever in many important particulars among which its insignificant death rate, the absence of jaundice and black vomit, the infrequency of hemorrhage and albuminuria and the correlation between the pulse rate and the temperature are of diagnostic value. Yet upon these very points experts have failed to agree in the differential diagnosis, as in the State of Texas during the epidemic of 1897. The difficulty is increased by the fact that yellow fever and dengue have the same habitat and very often prevail side by side.

Treatment.—There is no efficient prophylaxis as regards the individual in infected localities. Quarantine is ineffectual. There is no abortive treatment. The management of the individual case is entirely symptomatic. Hydrotherapy may be employed. The salicylates, aspirin, and the coal tar derivatives may relieve the pain. Opium, however, is usually essential. Potassium iodid and tonics may be given during convalescence.

YELLOW FEVER

By JULIUS L. SALINGER, PHILADELPHIA

YELLOW FEVER is an acute, specific, infectious disease, of short duration, which is epidemic in many tropic and subtropic countries. It is characterized by great depression, marked gastric symptoms, particularly vomiting of black, clotted blood, and by a yellow discoloration of the skin; pathologically, by gross degenerative changes, particularly in the liver and the kidneys. As a rule, one attack confers immunity.

The disease is known by a variety of synonyms which, however, as a rule, are the equivalents of yellow fever or black vomit in all languages.

HISTORY OF THE DISEASE

But little is known regarding the first appearance, the time and locality in which the disease occurred. Some authors have looked upon the pest which occurred 432 B. C., during the Peloponnesian war in Athens as yellow fever. This view, however, is not tenable. It may be maintained with certainty that yellow fever was noted for the first time after the discovery of America and that the cradle of the disease was situated in the countries bordering on the Caribbean Sea.¹ It is quite possible that yellow fever existed in those regions before the appearance of Europeans upon the American Continent, and it is quite likely that this disease was synonymous with the *cocolitzle* of the Mexican inhabitants or of the *poulicantina* of the Caribbeans, the original inhabitants of the Antilles. The Spanish historian Oviedo,² Gomara, and Herrera describe a dangerous malady occurring among the Europeans that accompanied Columbus upon his second voyage and which showed an extraordinary mortality. Oviedo states: "A pest arose among the Spaniards which was very contagious, due to the great dampness of the country; those that recovered were affected by incurable diseases and among those that returned to Spain there were many whose faces showed a yellow, saffron-like discoloration." Herrera states: "The sick were so yellow that they appeared as if painted a saffron color." It is, therefore, probable that the first authentic record of the occurrence of yellow fever in Europeans occurred in 1495, among the Spaniards that occupied the Island of San Domingo, and this view is all the more probable on account of the great epidemic distribution, the high mortality and the fact that the appearance of the disease occurred in several

¹ Sodr  and Couto, Yellow Fever, Nothnagel's Special Pathology and Therapy, vol. v, ii.

² La historia general de las Indias, Madrid, 1547.

succeeding years and in different districts among the recently arriving Europeans, whereas it spared those that were already acclimated.¹

From this time on, there are frequent notes in literature regarding an affection which we now recognize as yellow fever. It is true, not all of those diseases which attacked the Europeans who landed in America can be said to have been yellow fever, no doubt many of the diseases may be correctly referred to a malarial infection, it being well known that some forms of æstivo-autumnal malarial fever have many symptoms in common with yellow fever. The disease first appeared in Europe in the eighteenth century, and from that time on many well marked epidemics have been recorded.

The geographical distribution of the disease upon the American continent shows that cases have occurred as far north as Portsmouth, N. H., and more than thirty epidemics of yellow fever have been noted in Charleston, S. C., in the course of the nineteenth century.

The absolute distribution of yellow fever upon the American continent includes the zone between 46° 48' north latitude (Quebec) to 35° south latitude (Buenos Ayres), but within these limits there are many districts in which yellow fever never prevails. A zone in America in which the affection is almost always present extends from the 33° north latitude (Charleston) to the 24° south latitude (Santos).

ETIOLOGY

The etiology of yellow fever has for a long time been the subject of comprehensive studies. Since the introduction of bacteriology, numerous endeavors have been made to discover the specific organism of yellow fever, but it cannot be maintained with certainty as yet that the pathogenic organism has been discovered. The report of the French Yellow Fever Commission operating at Rio de Janeiro, Brazil, published in the *Annals of the Pasteur Institute*, November, 1903, states: "Neither in the mosquito nor in the blood have we succeeded up to this time in discovering the causative agent of yellow fever." The announcement by Dr. Sanarelli, in 1897, of his discovery of the specific agent of yellow fever, in the form of a bacillus which he termed *bacillus icterodes*, is now generally discredited. Dr. James Carroll² makes the following statement:

"Early in 1900, yellow fever appeared among the American troops at Havana, and during the summer it became quite prevalent among the Americans and Spaniards in and about the city. In order to take advantage of the opportunity offered for continuing the study of the etiology of the disease, a Board of Army Medical Officers was ordered to meet at Havana for the purpose. It was composed of Major Walter Reed, Surgeon, U. S. Army, the writer, and Dr. Jesse M. Lazear, non-immunes, and Dr. Aristides Agramonte, a Cuban immune. The three last named were contract surgeons. Dr. Agramonte and Dr. Lazear were already on the island; Dr. Reed and the writer arrived at Havana, June 25, 1900, and within a day or two the board was

¹ *Sodré and Couto, loc. cit.*

² *New York Medical Journal and Philadelphia Medical Journal*, February 6 and 13, 1904.

organized and work begun. Cultures from the blood of eighteen patients drawn during life were carefully studied, and from these, as well as from cultures made at eleven autopsies, the board failed to recover bacillus icteroides; the conclusion was drawn, therefore, that the organism could be excluded from further consideration."

In 1881 Dr. Carlos Finlay proposed a theory that the transmission of the disease was due to the mosquito, this view was neglected for a long time but, with the development of our knowledge regarding the part played by the mosquito in the transmission of malarial fever and on account of many points of similarity between the two affections, malaria and yellow fever, such as the prevalence in regard to season, the zone in which it prevails, and the way in which extension of the affection occurs, the subject was taken up again. After much laborious work and by unobjectionable experiments it was determined that the mosquito, the *stegomyia fasciata*, transmits the disease. This was not only proven by the Commission of a Board of Army Medical Officers, which consisted of Dr. Reed, Dr. Lazear, Dr. Agramonte, and Dr. Carroll, but was also confirmed by the French Yellow Fever Commission previously referred to. Dr. Carroll¹ writes:

"On the afternoon of July 27, 1900, I subjected myself to the bite of an infected mosquito applied by Dr. Lazear. The insect which had been hatched and reared in the laboratory, had been caused to feed upon four cases of yellow fever, two of them severe, and two mild. The first patient, a severe case, was bitten twelve days before; the second, third, and fourth patients had been bitten six, four, and two days previously, and these cases were in character, mild, severe, and mild, respectively. In writing to Dr. Reed that night of the incident, I remarked jokingly that if there were anything in the mosquito theory I should have a good dose. And so it happened. After having slight premonitory symptoms for two days I was taken sick on August 31st, and on September 1st, I was carried to the yellow fever camp. My life was in the balance for three days and my chart shows that on the fifth, sixth, and seventh days my urine contained eight-tenths and nine-tenths of moist albumin. The tests were made by Dr. Lazear. I mention this particularly because the result obtained in this case does not agree with the twentieth conclusion of Marchoux, Salimbeni, and Simond, that the longer the interval that elapses after infection of the mosquito the more dangerous he becomes. Twelve days, the period above cited, is the shortest time in which the mosquito has been proven to be capable of conveying the infection. It is my opinion that the susceptibility of the individual bitten is a much more potent factor in determining the severity of an attack than the duration of the infection in the mosquito, or the number of mosquitoes applied. On the day that I was taken sick, August 31, 1900, Dr. Lazear applied the same mosquito, with three others, to another individual who suffered a comparatively mild attack and was well before I had left my bed. It so happened that I was the first person in whom the mosquito was proven to convey the disease."

Dr. Lazear of the American Commission and Dr. Myers of the Liverpool

¹ New York Medical Journal and Philadelphia Medical Journal, February 6 and 13, 1904.

Commission both died of yellow fever from the bites of infected mosquitoes, thus two names must be added to the already large roll of martyrs of science.

Yellow fever is a disease of coast countries, rarely occurring in regions 1,500 feet above the sea level. The development of the disease is favored by filth, crowding of population, poor housing, hot season, and great humidity.

The view that the disease is transmitted by fomites has been almost entirely abandoned, owing to the experiments of the Yellow Fever Commission of the United States Army. There is great difference in the individual susceptibility to contract yellow fever, most authors agree that the negro race is less susceptible than the white race, this manifesting itself by the milder character of the disease in the negro than in the white. Males are more often attacked than females, and newcomers who are not acclimated usually acquire the disease readily. Guitéras ascribes the immunity of the natives in a yellow fever zone to the fact that they have passed through an attack of yellow fever in infancy or childhood, thus being protected by a subsequent immunity. He maintains that in tropical and subtropical regions in which yellow fever exists it is essentially an infection of childhood. The conclusions from the original results of the United States Army Yellow Fever Commission are as follows:¹

1. *Bacillus icteroides*, Sanarelli, and the hog cholera bacillus are practically identical.

2. Yellow fever is transmitted by the mosquito *Stegomyia fasciata*.

3. This mosquito may convey the disease as early as on the twelfth day after biting the patient, and it may retain the power to do so as long as it lives.

4. Yellow fever can be transmitted by the hypodermic injection of blood drawn from a patient in the first, second, or fourth days of the disease.

5. Yellow fever is not communicated by fomites.

6. The infectious agent of yellow fever can be passed through a filter that is impermeable to ordinary bacteria.

7. The infectious property of blood drawn from yellow fever patients is destroyed by a temperature of 55° C., maintained for ten minutes.

The disease is not contagious and there appears to be but slight risk in those nursing yellow fever patients. The *period of incubation* varies greatly, in general it is from one to seven days, in some cases even a little longer than this.

PATHOLOGICAL ANATOMY

The cadaver of one dying of yellow fever, in the majority of cases, shows a yellow discoloration of the skin. Frequently there are cyanotic areas and ecchymoses noted, these appear most prominently upon the face, chest, hands, and toes; often from the mouth, the nose, and from the anus a black fluid may be noted which may have coagulated (black vomit). The cerebral meninges show but little that is characteristic, the vessels are filled with black blood, the ventricles of the brain show a yellowish discoloration of the cerebro-spinal

¹ New York Medical Journal and Philadelphia Medical Journal, February 6 and 13, 1904.

fluid. The cerebral cortex, as a rule, retains its normal color, but may show punctate areas of hemorrhage. The pyramidal cells of the pons and medulla are said to show the phenomena of peripheral chromatolysis. The pericardium shows a collection of fluid which varies in regard to amount, color, and composition. The analysis of this fluid gives a positive reaction for bile and sometimes also for hemoglobin. There is marked fatty degeneration of the cellular tissue of the posterior surface of the sternum and mediastinum, which is noted at once upon opening the thorax.

The heart is soft and flabby, especially the right ventricle, whereas the left ventricle is often of a tough consistence. Most conspicuous after opening the pericardium is the fatty degeneration of the heart which is particularly marked in the right ventricle. Upon the surface of the heart, even in the fatty layers, hemorrhagic areas are noted, which vary in size from punctate areas to large ecchymoses. The blood vessels beginning at the aorta are sometimes stained by bile acids. There are no characteristic changes in the pleura. The lungs, in the majority of cases, show no lesions that are characteristic.

The stomach, in the majority of cases, shows marked alterations; there is usually a high-graded dilation, the mucous membrane is softened, thickened, and uniformly congested. The color of the mucous membrane varies from a normal pale red, upon a grayish-white base, to a dark red color. Apart from superficial black areas in the deeper structures of the mucous membrane, disseminated ecchymotic plaques are noted. The stomach is rarely found empty, there is a fluid residue which contains undigested food, drugs, and blackish threads; this fluid corresponds to the black vomit which is clinically noted during the course of the disease. The small intestine shows lesions which correspond to those occurring in the stomach. The large intestine is unaltered.

The liver shows profound alteration, most conspicuous is the change from its normal color. All shades of yellow, from pale yellow to an intense dark yellow, are noted, the liver having acquired the name of the boxwood liver. As a rule, the organ is increased in size, especially the right lobe. The liver is often adherent to the surrounding organs, which is particularly noted in the protracted cases. As a rule, the gall-bladder is empty or contains but slight amounts of a bottle-green, blackish, sticky fluid of a syrupy consistence. The capsule of the liver may readily be peeled from the parenchyma, sometimes adhesions are noted. The liver is coarse, hard, elastic, and friable. The cells are in all stages of fatty degeneration, and areas of necrosis are readily detected.

The kidneys show the changes of acute diffuse nephritis. The volume of the organ is normal or increased in size, the color usually pale. The protoplasm of the epithelium of the convoluted tubules is swollen and shows fatty granular degeneration; this may even be noted in the entire organ.

The spleen is but rarely altered, it is usually normal in size and if found enlarged the increase in volume is but moderate; the external appearance of the organ is unaltered.

The pancreas is increased in size, its color is yellowish, the epithelium of the glands shows granular fatty degeneration.

The pathologico-anatomical changes of yellow fever consist principally in a general acute fatty degeneration.

SYMPTOMS

The onset of the disease is sudden, without prodromes, as a rule. Where prodromes occur they consist of nausea, anorexia, lassitude and general malaise. The affection commonly begins in the early morning, either a severe chill being present or successive chilly sensations taking its place. The chill is accompanied with severe headache, pains in the dorso-lumbar region, and sensations of heat. The temperature rises suddenly to 104° F. or even to 105° F. and even higher. The pulse is full, tense, increased in rapidity from 100 to 120 beats per minute. There is severe headache, either unilateral or bilateral, affecting particularly the temporal region, more rarely confined to the occipital region or other portions of the head. There is marked hyperemia of the face and of the conjunctiva, photophobia, and a peculiar expression of the face, which is of some importance in diagnosis. Nausea and vomiting during this period may be entirely absent, but in a day or two become manifest. Constipation is the rule. The tongue is coated toward the centre but the borders are clear. The apex beat of the heart is diffused and strong, the urine is decreased in amount, of a dark color, and as yet free from albumin, occasionally anuria may be present. The previously described symptoms are prominent for the next two or three days, to which there is gradually added somnolence or insomnia, and unquenchable thirst. At the end of the second or beginning of the third day new symptoms are added, the tongue shows a whitish coating, whereas the borders remain red; pressure upon the epigastrium develops pain, vomiting becomes prominent, it being impossible even for the patient to retain small quantities of water. Epistaxis may occur in this period and if an examination of the urine is now made albumin will be found present, which increases in amount usually from the second day of the disease on.

This stage is characterized as the *stage of onset*, the duration, upon the average, being from one to four days. It is followed by the second stage, *the stage of calm or remission*, which lasts from twenty-four to forty-eight hours. The temperature falls usually, however, still being a degree or two above the normal throughout this stage. The pulse becomes soft, easily compressible, from 80 to 100 per minute, the headache and muscular pains disappear, the hyperemia of the face is no longer noticeable but an orange yellow discoloration of the conjunctiva begins to be noted, and slight perspiration takes place. In rare cases this stage is succeeded by convalescence. This is, however, exceptional, nor does the stage of calm by any means occur in all cases. According to the latest investigations it is absent in the greatest majority of cases. If the stage of calm does not occur, the gastric intolerance continues, the vomiting becomes more pronounced and now the ominous black vomit makes its appearance. The vomited material often resembles coffee grounds, and becomes darker and denser after each attack of vomiting until it finally may be as black as ink, from which the disease receives one of its synonyms "*vomito negro*"; hemorrhages occur from other parts of the body, thus from the tongue and gums, from the intestine, from the uterus; and petechiæ appear in the skin.

The conjunctivae become more and more yellow and this yellow color, sometimes being as intense as saffron, appears not only in the face but over the entire body. This color is due to urobilin, bilirubin, and biliverdin, which may be detected in the blood serum and in the urine by chemical and spectroscopic analyses.

The liver increases in size, the epigastric region is tender, which has been described by many authors as "epigastric fear," this usually is the premonitory sign of the subsequent black vomit. Often there is severe hiccough which markedly disturbs the rest of the patient.

Condition of the Blood.—As a rule, there is an increase in hemoglobin, which is continuous, beginning in the course of the first day of the disease, increasing upon the second, and in severe cases lasting until death occurs. In favorable cases, with the onset of improvement, the amount of hemoglobin decreases and during convalescence is decidedly below normal. The erythrocytes do not increase in the same proportion, which shows that in yellow fever the hemoglobin contents of the individual red blood corpuscles is increased. In severe cases there is a hypoleukocytosis, the average number of leukocytes varies from 3,000 to 5,000. In favorable cases the number of leukocytes increases, in unfavorable cases leukopenia becomes more marked. In convalescence, as a rule, there is a slight leukocytosis.

The urine is decreased in amount, it contains large quantities of albumin but is of an acid reaction. In this stage anuria with subsequent uremia may occur. The apex beat of the heart diminishes in power and may become imperceptible. The pulse is soft, small, readily compressible, and gradually bradycardia occurs, so that in some cases a pulse beat of only 30 or 40 per minute has been observed.

Occasionally eruptions occur, such as erythema, urticaria, herpes facialis, and even eruptions showing a pustular character. The symptoms on the part of the nervous system consist of restless sleep, which is followed by complete insomnia, then low muttering delirium may occur, and even sometimes delirium of an active character. In the third stage the temperature varies between 100° F. and 101° F.

At this stage in the affection, various changes may occur so that different clinical pictures may present themselves which have been accurately described by Sodré and Couto.¹

1. The previously described symptoms gradually decline after they have been present for two or three days. The urine becomes clearer, and more copious in amount, the excretion of bile coloring material and albumin disappears, the sensation of epigastric fear lessens, vomiting ceases, the tongue loses its coating and becomes red and moist; the hemorrhages cease, the heart regains its power and sleep returns. All other symptoms decline in a similar manner, convalescence begins, and the patient is on the high road to recovery.

2. It often occurs that the urine which has been scant, turbid, and which contains large amounts of albumin, rapidly, almost from minute to minute, decreases in amount, becoming more turbid and containing still larger quantities of albumin. After a few hours but very small amounts may be drawn

¹ *Nothnagel's Special Pathology and Therapy*, vol. v, ii.

from the bladder by means of the catheter, finally, the secretion of urine ceases entirely. Anuria has occurred and this is an especially serious symptom in yellow fever, for in proportion to the amount of urine, the accompanying symptoms of renal insufficiency appear—arrhythmic dyspnea, jactitation, spasms of the muscles of the face and eyes, subsultus tendinum, etc.—finally, the condition gives way to the symptoms of true uremia—eclampsia, delirium, coma.

3. At other times hemorrhages dominate the scene. Often, although not always, introduced by epigastric fear, black vomit becomes more copious and more frequent—gastric and intestinal hemorrhages, epistaxis, do not cease—menorrhagia and other profuse hemorrhages appear. The pulse is small, soft, and rapid, delirium, insomnia, and unrest are present. Death occurs in collapse unless the hemorrhages are allayed by drug treatment.

4. In other cases the renal function remains normal and the hemorrhages are by no means intense nor of a character dangerous to life, nevertheless, marked jaundice occurs, the skin being of an ocher or saffron color. The blood serum and urine are loaded with biliary pigments, the liver decidedly enlarges and is sensitive to pressure, continued and severe singultus disturbs the patient. The feces—provided they are not black—are clay-colored. The urine is profuse, intensely yellow or of a bottle-green color. The pulse is weak and slow, 60 to 90 per minute. The hemorrhages continue but are not profuse. This condition remains for a few days and then either ataxic adynamic phenomena occur, occasionally accompanied by the “typhoid state,” death occurring upon the eighth, tenth, or twelfth day, or the patient is attacked by convulsions and coma—and finally these symptoms may recede and give way to a protracted convalescence.

In other cases there is danger on the part of the heart. Adynamia continues, increases more and more, the pulse becomes very small and soft, more rapid, being 110 to 120, with a normal or subnormal temperature in the patient. Examination of the heart shows an absence of the impulse, the cardiac sounds are dull and may scarcely be discerned. This condition may improve and recovery occur, this is, however, not the rule. The tachycardia becomes enormous, the pulse is thready, the heart sounds can no longer be discerned. There is complete adynamia and collapse occurs which leads to the fatal issue.

5. The purely ataxic form is as rare in adults as it is common in children. In general the nervous symptoms occur during the first period of the disease, being very marked; there is delirium, unrest, or abnormal somnolence, these symptoms appearing simultaneously with the rise in temperature and with the other phenomena of the affection. In favorable cases this condition lasts two or three days, but in severe cases the active delirium is soon succeeded by an increasing coma. Subsultus tendinum, carphologia, tremor, twitching of the facial muscles, strabismus, contracted pupils, and photophobia occur; the respiration is irregular and toward the end the Cheyne-Stokes type may appear. In some cases the course of the affection is fulminant and may terminate in from thirty-six to forty-eight hours.

These forms have given rise to the five clinical varieties which are designated as, 1, the acholic or hepatic form; 2, the anuric, uremic, or renal form;

3, the hemorrhagic form; 4, the cardio-adyneic, cardio-asthenic, or cardiac form; and 5, the ataxic form.

Regarding the severity and intensity of the infection, the following varieties may be noted: *a*, an abortive form; *b*, a larval or undeveloped form; *c*, a mild form; *d*, a severe form; and *e*, a fulminant form.

COMPLICATIONS AND SEQUELS

The course of yellow fever is often interrupted by complications and sequels. Secondary infections in the third period of the disease are frequent (by the colon bacillus, streptococci, staphylococci, proteus, etc.). Septic endocarditis, pneumonia, gangrene, suppuration, erysipelas, lymphangitis, erythema, etc., may occur.

Some epidemic diseases may accompany yellow fever, such as enteric fever, influenza, malaria, and sunstroke. In the course of convalescence, paralyses and psychical disturbances have been noted, which may be looked upon as resulting conditions of the infection.

Relapses sometimes occur.

DIAGNOSIS

In regions in which the disease is endemic the diagnosis, as a rule, does not offer difficulties. Difficulties in the differential diagnosis arise when other diseases are epidemic at the same time. The disease may be confounded with dengue, malarial fever, and acute yellow atrophy.

DIFFERENTIAL DIAGNOSIS

The differential points from dengue may be discerned from the following table:

	DENGUE	YELLOW FEVER
Where occurring:	In tropic and subtropic countries.	In tropic and subtropic countries.
Numbers affected:	Large majority of population.	Cases limited.
Nature:	Contagious.	Contagious.
Duration of epidemic:	Two to five months.	Indefinite.
Affects whom:	All races.	Foreigners particularly.
Period of incubation:	Two to five days.	One to seven days.
Characteristics:	Severe pains in joints and muscles.	General muscular pains.
Ambulatory cases:	Frequent.	Rare.
Catarrhal symptoms:	Extremely rare.	No catarrhal symptoms.
Pneumonia or pleurisy:	Rare.	Rare.
Gastric symptoms:	Prominent.	Nausea and vomiting characteristic.
Diarrhea:	Rare.	Constipation.
Spleen:	Not enlarged.	Slightly enlarged.
Pulse and temperature:	Rapid and high fever.	Pulse slow and temperature not so high.
Eruptions:	Frequent.	Jaundice.
Hemorrhages:	Rare.	Common.
Albuminuria:	None.	Constant.
Mortality:	Low.	Very high.
Sequels:	Rare.	None.

From malaria, the affection is differentiated by the presence of the plasmodium in the blood in malarial fever and its absence in yellow fever, although it must be remembered that occasionally malaria and yellow fever occur in combination. This has the effect of rendering yellow fever more severe.

Acute yellow atrophy may be readily differentiated by the fact that it is more common in women, especially during pregnancy, that hemorrhages are not so liable to develop and that the liver rapidly decreases in size, and the urine in acute yellow atrophy contains leucin and tyrosin.

PROGNOSIS

Yellow fever is always a serious affection, the mortality in different epidemics has varied from 15 per cent. to 85 per cent. Alcoholics show a bad prognosis. Unfavorable symptoms are, a rise in temperature above 103° F. or 104° F. early in the disease, anuria, and marked development of nervous symptoms such as delirium, coma, and convulsions; black vomit, although very serious, is not necessarily a fatal omen. Symptoms from which a favorable prognosis may be made are, slight fever, absence of intense jaundice, slight hemorrhages, and copious urine.

PROPHYLAXIS

In view of the report of the United States Yellow Fever Commission and of the French Commission, efforts should be made to prevent the spread of the disease through infected mosquitoes. This may be done by protecting the sick from the bites of mosquitoes, protecting houses by means of screens, and mosquito-nets, by destroying the insects and larva in the houses, and by the prevention of the breeding of mosquitoes in the vicinity.

Quarantine is still carried out in many countries, its efficacy, however, is questioned by the best of authorities.

TREATMENT

There is no known remedy which will abort or cure yellow fever. No drugs appear to possess the slightest influence upon the pathological process. Recovery occurs spontaneously in about 50 per cent. of the cases, no matter what form of treatment is adopted. Sanarelli's serum treatment has been almost entirely abandoned. Among the remedies which are most widely used in the treatment of yellow fever are quinine and sodium salicylate. Upon careful study, it has been shown that the salts of quinine are rather harmful than useful and have only shown beneficial effects in those cases in which malaria and yellow fever coexisted. Sodium salicylate has only been found efficacious in benign cases which would have recovered under any other form of treatment (Sodré and Couto).

The majority of physicians in tropical countries in which yellow fever is endemic advise an active expectant treatment. Upon the first day of the disease in all cases diaphoretics and laxatives are administered. Thus, in

mild cases, a mustard foot bath and warm drinks or ammonium acetate are employed. If the case is more severe, if there is decided fever and marked pain, besides the mustard foot bath and local sinapisms, either of the following formulæ are prescribed:

R	Aq. filtrat.....	120.0
	Rhum Jamaic.....	30.0
	Antipyrini.....	3.0
	Tct. Aconiti gtts.....	xvi
	Syrup. flor. Aurant.....	30.0

S.: Tablespoonful every hour.

Or,

R	Julep gummos.....	120.0
	Natrii salicyl.....	5.0
	Antipyrini.....	3.0
	Tct. Aconiti gtts.....	xvi
	Syrup. flor. Aurant.....	30.0

S.: Tablespoonful every hour.

This treatment is discontinued after profuse diaphoresis has occurred and now a purgative is administered. Calomel is preferred by many, either given in one dose of $7\frac{1}{2}$ grains ($\frac{1}{2}$ gram) and followed by castor oil, or if the patient cannot take castor oil, rhubarb or cascara sagrada are given in its place. Acid drinks are administered and the third stage of the disease is awaited. A restricted diet is given from the onset and if vomiting is continuous or frequently repeated the lemonade is discontinued and sinapisms are applied to the epigastrium and enemata of luke-warm water are ordered. In case of long-continued vomiting or with decided nausea, cocaine in small doses is useful. In some cases in which the fever is high cold baths, sponging with cold water, and application of ice to the head, are recommended.

When black vomit occurs sesquichloride of iron, ergot, acetate of lead, and opium are recommended but no drug can be depended upon to check the hemorrhage. When the action of the heart becomes feeble, stimulants are necessary. The uremic symptoms are treated by hot baths.

In convalescence the patient must be carefully fed and tonics are indicated. Complications must be treated upon general principles.

INFLUENZA

By P. FÜRBRINGER, BERLIN

ETIOLOGY

A LITTLE more than a decade has passed since our views regarding the nature and manifestations of grippe have experienced an unexpected amplification, a thorough change. The pandemic of the winter of 1889 and 1890, which is still generally remembered, forms the landmark of more exhaustive knowledge. Naturally, we must not underrate what was contained in literature previous to this time, as we there find notable depictions of the epidemic dissemination of the disease, especially its pandemic distribution, at the beginning of the fourth decade of the nineteenth century, in Vienna and Europe, and also true and vigorous explanations of the clinical picture, which betray great power of discernment. But, in the same manner as in the latter, frequent, but less important, epidemics of influenza did not then attract the general medical interest, so also have its text-book descriptions become less frequent. In fact the classification of grippe among the infectious diseases had been given up entirely, it being only supplementarily mentioned as a peculiar form of bronchial catarrh. Thus von Niemeyer's text-book of Special Pathology and Therapy, which twenty-five years ago was considered a reliable guide, defines influenza as bronchial catarrh, which, accompanied with an unusually severe general affection, presents a certain similarity with acute exanthems and occurs in epidemics; the latter develop under the influence of unknown atmospheric or telluric conditions; nevertheless, an infection was considered to be doubtful.

This has become entirely changed since the disease has made its turbulent tour around the world, and since the malady, on its travels from east to west has awakened physicians, the most of whom had never known true grippe or had completely forgotten it. The extent of investigation and work that has been done since then can be inferred from the fact that the publication "The Influenza Epidemic of 1889-90," which was prepared by order of the Berlin Society of Internal Medicine, at the instigation of its first president, von Leyden, mentions, for these two years alone, over 1,000 contributions referring to it. These numerous publications were followed up to the present time by quite a number of others, for influenza has never become extinct since the occurrence of the above mentioned pandemic. Continually recurring epidemics, although of a smaller extent, of which I mention those of the winter of 1891-92 and the beginning of the winter of 1895, unceasingly furnish material for further complementary observations by authors and practitioners.

The result of these untiring investigations has primarily given us positive information regarding the general character of the affection. We know now that influenza is a peculiar acute infectious disease, the occurrence of which cannot be conceived without the participation of an organized generator. It is probable that this pathogenic organism has already been discovered; I say probable, for it is true the microorganism which is named after its discoverer and called Pfeiffer's bacillus, which we have known for eight years, is found constantly and exclusively in influenza, but the animal experiment has not given absolute proof so that it cannot be maintained with certainty that the influenza bacillus is the only organism producing the disease.

Unfortunately, the profession is not able to derive any actual benefit from this scientifically important discovery; at any rate THE INFLUENZA BACILLUS cannot claim nearly the same significance as the tubercle bacillus as a criterion at the bedside. Principally not because a positive differentiation from similar bacilli is impossible microscopically; in the first place, the shape—very short and thin rods with rounded ends—does not present any particular characteristics, and, furthermore, its staining properties—mostly more markedly stained end-poles, not staining after Gram—cannot be considered as specific. Nevertheless, we are far from pronouncing the microscopical research for the influenza bacillus to be without value. The rods are found at the autopsy, especially when death has occurred during the acme of the disease, very often in the catarrhal secretion of the smaller bronchi, frequently in actual pure culture, in part enclosed in pus corpuscles. Such findings may be considered demonstrative. The conditions are different upon examination of the sputum, which, as is well known, is very rarely free from accompanying bacteria. Besides, in quite a number of cases, the influenza bacilli disappear extremely rapidly from the sputum. The resort to culture for purposes of differentiation must be restricted essentially to laboratories, as the usual culture media are not capable of causing a growth of this stubborn bacillus. Not until hemoglobin (especially pigeon blood) was employed did the experiment furnish small, bright, structureless columns. It follows, therefore, that the diagnosis of influenza by means of bacteriology is not commonly possible by practising physicians, and cannot become so for the present; it is quite conceivable, therefore, that hospitals gave up looking for them on account of the frequent disappointments when attempting to decide the diagnosis by the demonstration of true influenza staffs or rods. Even a pseudoinfluenza bacillus must be taken into consideration, as we know of cases in which, by the "demonstration" of the alleged pathogenic organisms, the originally correct diagnosis became doubtful. Naturally, such occurrences do not detract from the value of the scientific discovery as such.

A controversy, which is not concluded as yet, has raised the question as to the dissemination of this infectious disease. The Society of Internal Medicine of Berlin, in the meetings of December, 1889, bore witness to the extremely lively exchange of opinions, especially regarding the contagiousness and infectiousness of influenza, but no conclusion was reached, one party claiming contagion, the other miasma as a causative factor! And even at present, after long intervals of peace between the debates, no final verdict has been reached. But it has been recognized that, especially with the undisputed pre-

sumption that the natural infection of man takes place, in the majority of cases, by inhalation, a sharp demarcation between "contagious" and "miasmatic" dissemination should not be attempted. In fact, the question as to the existence of the pure miasma has for obvious reasons become subject to an increasing variation of opinion. It might be permissible to speak of a contagio-miasmatic dissemination, in contrast to a purely contagious one. Both methods still have their firm supporters in spite of the discovery by bacteriology, that the influenza bacilli perish rapidly, both upon drying and in water. The previously mentioned collective investigations show that about 1,500 physicians were in favor of, 1,100 against this view of contagion. Even this comparatively small difference is food for thought. Personally, I was not quite able at the time to acknowledge an essentially contagious dissemination of the disease. This attitude was determined especially by the personal experience that, in the Friedrichshain Hospital, the medical wards of which contained influenza patients in every room, the other patients, at least the majority of them, remained free from infection for a long period. In view of the surely brief *period of incubation* of the infection—the best authors assume, for good reasons, an average of one day, often a fraction of a day might be sufficient, several days truly an exception—and the general predisposition to the disease, such a fact, which is also confirmed by other experienced physicians, would not be comprehensible if a manner of propagation which would correspond to about that of the acute exanthems would be admitted to be the only one. The frequent fact also must be taken into consideration, that human beings who are remote from all communication, thus ships' crews on the high seas, are suddenly, without warning, attacked by the malady; it actually forces us to acknowledge that the disease is not always disseminated by contagion. If the development of the course of the malady is to be made familiar to human comprehension, we would say that the germs must fill the air over land and sea in enormous quantities "as though scattered from a gigantic box of Pandora." On the other hand, it is true, the appearance of influenza in secluded retreats (convents, prisons) and in houses which are remote from traffic, so soon as a person afflicted with grippe has entered, is greatly in favor of contagion from person to person. The opinions are justified in that quickly as influenza epidemics travel, it must appear questionable in most cases whether the rapidity of locomotives and steamships actually is greater than the speed of the disease. *At any rate an essential dependence of the dissemination of influenza epidemics upon human intercourse must be admitted.*

Regarding epidemics of the disease in respect to the influence of locality and meteorological conditions, the literature contains a comprehensive number of reports, naturally, there is also much that is hypothetical. It is not my intention to even enumerate their outlines. In limiting myself to calling special attention to the graphic depictions of the occurrence and course, especially of the above-named pandemic, as they are given, for instance in the elaboration of the Swiss Board of Health, I will only mention the sunlight theory which has been repeatedly brought forward by practitioners. The greater the deficiency of sunlight, the more favorable the growth of the influenza bacilli. It is conceivable that such a demonstration is bound to

meet with the greatest of difficulties. On the other hand, I do not consider the rejection of such a dependence admissible in view of the occurrence of the majority of epidemics in the gloomy days of the winter.

The majority of physicians have had an opportunity to become convinced of the almost universal prevalent *predisposition* to influenza. As a matter of fact, only nurslings, and a very small minority of favored persons, may be considered exempt. The idea of acquiring a certain immunity by once having been attacked with the malady has long since been maintained by experienced clinicians. This is true, in spite of the generally justified apprehension of numerous individuals who have been taught by experience, "that their turn would come again" with the next epidemic. But upon closer investigation we cannot help observing that the *attenuation of the affection* plays an important part. Countless intelligent and unbiased patients have assured me, and I have observed it in my own person, that later affections manifest themselves at a time when the disease is epidemic, in comparatively more mild and rudimentary degree, "*formes frustes*." If in the first pandemic the patient was caused to become bedridden, in later attacks he was enabled to attend to his duties both at home and abroad. It is true, particular caution is necessary in judging this question, which I find is treated of very sparingly in literature, in spite of its practical significance, owing to the uncertainty of a positive diagnosis in a great many cases. If those cases were excluded which the laity consider influenza, such in which all possible forms of respiratory catarrh with marked malaise are present, and also those in which there is a reasonable doubt, a sufficient number of cases still remain to show the truth of the previously mentioned attenuation. Naturally, in influenza, with its rapidly subsiding epidemics, the conception of immunity can only be maintained for a limited time. Bacteriologists are already prophesying that another pandemic is due, and this on account of the discovery of a disproportion between the ability of determining the influenza bacillus and the toxemia in the last epidemics.

SYMPTOMS

In describing the *clinical picture*, it is obvious that only the principal points can be dwelt upon. The depiction of an infectious disease which scarcely spares a single organ, with its complications and sequelæ, which even creates the greatest varieties within a single organ, compels me to enlarge particularly upon that form which predominates, and which has given its stamp and impress to our general views regarding the affection, namely the catarrhal, especially the *respiratory catarrhal* form. It is true, an adherence particularly to this mode of manifestation, has narrowed, in fact misguided the opinions of physicians too much, until the cyclone of the great pandemic revealed new views and taught us that the general affection designates the character of influenza in a much more determining manner than the respiratory catarrh. And yet, particularly the latter, the inflammation of the mucous membrane, plays the principal part in a clinical respect, this frequently extending from the tip of the nose to the innermost bronchi, and, what is still more important, the extension of the catarrhal process of the lung and pleura forms not only the most frequent basis for the dangers of the disease

but also creates clinical and anatomical peculiarities which, on account of being most studied, are bound to claim the interest of the physician primarily.

But before entering upon this discussion, I desire to call attention to the primary *onset* of the disease and its *febrile course*. The usual mode of appearance, fully described in all text-books, is familiar to all, viz., the suddenness of the onset of severe symptoms, the tormenting pains in the head, especially behind the eyes, in the vertebral column and in the limbs, the sensation of general lassitude, in fact prostration, the cough which appears to still more irritate the patient and aggravate the disturbance, the disagreeable loss of appetite, the insomnia. To these is added another symptom, the *very red flushed face*, upon which, according to my opinion, not sufficient stress is laid in literature, although it manifests itself strikingly to the physician and to the relatives of the patient. If influenza patients who are in the same ward with the febrile cases are observed, this appearance of the face, even at a distance, is not so readily forgotten. The condition most nearly resembles the facies of scarlatina, but in influenza the pallor of the forehead and the region about the mouth is absent. It is obvious, in view of the frequency with which a flushed face (it is true limited mostly to the cheeks) generally manifests itself, and on account of the occasional absence of the same in influenza, that we cannot speak of it as a pathognomonic symptom. But whoever endeavors to acquire precision in observation, and directs his attention to graduated differences, will be suspicious of genuine grippe in a great number of cases, even with this first, conspicuous impression.

At this point I must refer to a second peculiarity which is very pronounced in the face, in fact, sometimes even found exclusively there, viz., a yellowish discoloration, a slight jaundice, which, although it has not escaped the notice of the physician, is not sufficiently appreciated. Although, in spite of my having closely examined hundreds of cases for this symptom, I am not able to confirm that this icteroid discoloration is found in an overwhelming majority of cases, an essential positive percentage remains which is large enough to ascribe a distinct significance to the same. In fact, attention was called to this a number of years ago. The slight jaundice, even if it is always observed without distinct urinary findings—only rarely was I able to determine a positive result with the Gmelin reaction, a slight yellowish froth of the urine—furnishes another proof that our disease indicates much more than an infectious febrile bronchial catarrh. It presupposes a *far-reaching alteration of the blood*. It is probably correct to refer to this alteration, the marked debility, and the great disturbance to which the vaso-motor apparatus of the influenza patients so often are subject, which manifests itself in a pronounced and very conspicuous tendency to *hemorrhage* from various organs. We observe, to a greater extent than in the acute exanthemata and in other acute infectious diseases, the hemorrhagic character of various secretions and excretions, especially of the saliva (from the gums), of the sputum, even without pneumonia (for timid persons, often a reason to fear tuberculosis), of the urine, and of the feces. True, dangerous hemorrhages from the mucous membranes (epistaxis, metrorrhagia) give rise to great concern, not only to the patient but also to the physician; finally, marked forms of purpura are not wanting, and even at the autopsy our interest is aroused by the hemorrhagic

condition of this or that pathological process in an organ. Possibly that form of acute hemorrhagic inflammation of the brain should be considered the most severe of which I could give the first more detailed clinical and anatomical report, owing to the admission of a number of patients with this affection to the Friedrichshain Hospital. According to the facts, there could be no doubt that this "flea-bite-encephalitis," as I thought of designating it from a rapid characterization of the autopsy finding, represented a complication of influenza in the case described. It is well known that acute hemorrhagic encephalitis is also observed as a primary affection.

From text-book descriptions and from monographs, it is well known that besides the common, most frequent catarrhal form of the disease, "*gastro-intestinal, rheumatoid, typhoid, and nervous*" varieties of grippe have been observed. There can be no great objection to such a schematic classification, which is of value for correct differentiation, as the busy practitioner often actually encounters some forms which cannot at once be separated from gastro-enteritis, severe muscular and even articular rheumatism, and enteric fever; however, and this we should bear in mind, the comparative infrequency of true cases of catarrhal influenza is opposed by the overwhelming frequency of the most various *transitional* and *mixed* forms. I believe that I have seen every variety of combination which is possible with the above-named original form; in fact, a more or less important part of every variety could be discerned in some cases. But it is not necessary to enumerate complicated designations or even to establish further cardinal varieties.

The fever, an important attribute of this affection, in spite of quite a number of scarcely febrile, and some entirely afebrile, cases, has served as an object of exhaustive studies in numerous treatises. I do not think that these investigations have been able to essentially influence our views, derived from the first dozens of our own cases. The fact that at that time we purposely avoided interfering with the natural course of the fever by any antipyretic treatment, has enabled us from the clinical material at our disposal to easily draw conclusions as to certain important conditions. Accordingly, two types should be differentiated, in view of the fact that almost exclusively, medium severe and severe cases were admitted to the Friedrichshain Hospital, and that my personal opinion was required only in the most severe types of the disease: The brief attack of fever, lasting on an average from one to two days, showing a *single steep apex of the fever curve*, and the typhoid-like course which extends over half a week to a week, which is characterized by a *step-like curve*. For the first mentioned variety, I may mention my own infection as a paradigm because from the very onset I consulted the thermometer at regular intervals and minutely controlled the relations between the subjective manifestations and the curve of the fever: On December 1, 1889, I awoke at six A. M. in the best of health, toward eight o'clock I noticed, within a few minutes, a general, moderate but peculiar, sensation of illness, such as I had never felt before; in spite of this, my temperature was only 98.2° F.; therefore, true prodromes. At ten o'clock, with a slight chill upon leaving the house, the temperature rose to 99.3° F. with an increase of malaise, no local disorder. At noon the temperature was 101.3° F., at two o'clock 102.3° F., a sensation of oppression in the head, pronounced pain

behind the eyes, cough, lassitude, which symptoms greatly interfered with my daily work, loss of appetite. At four o'clock the temperature arose to 103.2° F.

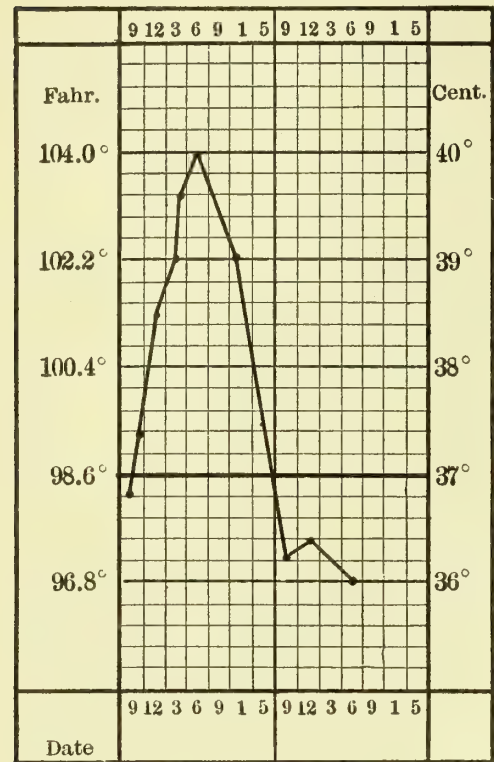


FIG. 1.

and I was scarcely able to perform any mental or physical labor. Two hours later I went to bed with a temperature of 104° F., almost unconscious, complaining of chills and heat, and pains in the small of the back, heavy feeling in the limbs, and violent cough which aggravated the headache to the utmost. I did not sleep. At midnight, a sudden perspiration appeared, temperature 102.2° F.; on the following morning the temperature was 97.2° F., the pains had entirely disappeared but considerable weakness remained. In the afternoon of the same day I was able to leave my bed and on the following day I resumed my professional duties, but an irksome sensation of weakness, irritable cough, and dyspepsia remained for about a week, and not until the last day of the year did I feel "myself again." If a curve of this uncomplicated case is constructed the attack of fever shows a single steep rise which did not even last

twenty-four hours (see Fig. 1). However, it would be wrong to believe that the majority of cases, provided complications did not occur, would even approximately adhere to this type or to the second one, but rather the most

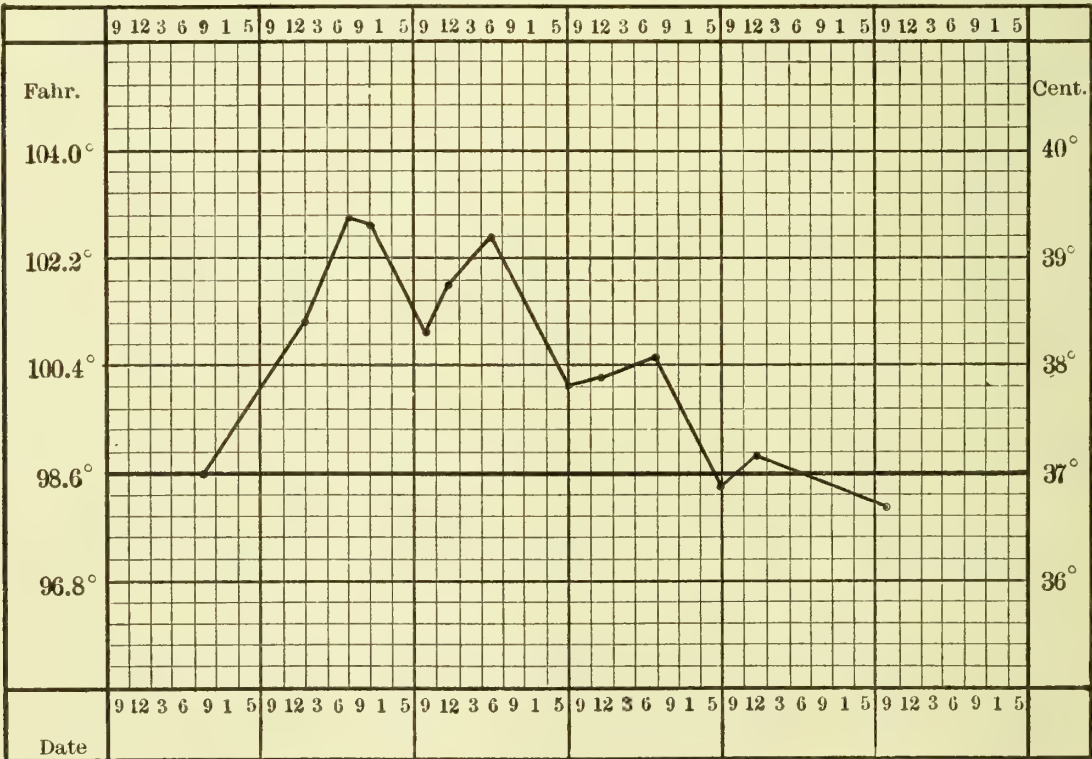


FIG. 2.

varied mixed forms of both varieties would be found to represent the lion's share. Frequently the steep, abrupt ascent and the step-like decline were

probably combined, as can be seen from the second curve which represents the case of my wife (Fig. 2). The curve is very apt, after two or three days, to fall to normal or even below, for about one day, to ascend again although no complications take place; a true relapse therefore.

Let us now consider the severe, dreaded **pulmonary complications**. I shall never forget the dismal picture which our hospital wards presented about New Year's time of 1890; a frightful number of the severest *pneumonias* of an asthenic type, of which a large proportion, in spite of the labors of physicians and nurses, sooner or later found their way to the post mortem table. Clinical and anatomical observation was soon rewarded by noting many surprising changes which previously were rarely seen. In the first place, the fact that, besides a number of influenza patients who brought their catarrhal and pulmonary inflammations with them as obvious complications of influenza, a surprisingly large number of true croupous pneumonias were admitted, greater even than we had been used to admitting. This increase was staggering to even the most experienced physicians of the city. They were in doubt whether they were dealing with substantive forms of the disease or whether the latter were due to the extensive epidemic of grippe. This question has concerned us greatly and has not been settled finally as yet, despite the interest and the many investigations on the part of a number of authors—for the same fact was experienced in other localities and recurred during the late epidemics of influenza, although to a less degree. The belief that this was a mere coincidence prevailed but had soon to be abandoned owing to the tenacious recurrence of this combination. Instead, the parallelism of the condition was referred to the not infrequent combination of two or more acute infectious diseases, occurring side by side. Lately there is a tendency to immediately connect the fibrinous pneumonias with the infection by influenza, in that, while ascribing their original cause to the activity of the pneumococcus, the symbiosis of the influenza bacillus is, however, necessary. Therefore, not a genuine croupous pneumonia but the product of mixed infection! As such exceedingly often, probably in the majority of cases, it fails to conceal its peculiar clinical deviations from the type of true fibrinous pneumonia: Instead of pneumonic sputum, the muco-purulent form; in place of extensive lobar infiltration, more limited areas of consolidation which even the expert is often compelled to search for; not a brief curve of the fever with a high range and critical defervescence, but a protracted, dragging course with marked remissions; finally, a pronounced disproportion between the local process and the cardiac involvement, and of the respiratory difficulty, genuine "asthenic" pneumonia, with a threatened weakness on the part of the heart and dyspnea.

It is true, there still remain a conspicuous number of regular true croupous pneumonias, which may be fully explained as such, and which, on account of their difficult course, bear no resemblance to those of influenza. The number of these pneumonias which are essentially concerned in the peculiar increase of frequency is so great that, apart from the absence of influenza bacilli in the sputum, I should unrestrictedly deny an intimate connection with grippe infection.

The conditions are different, however, with true INFLUENZA PNEUMONIA,

such as we observe in greater frequency as true complications of influenza, these are particularly *bronchopneumonias*. The process is inseparably associated with immigration of the generators of influenza belonging to the influenza infection, in quite the same manner as the catarrhal pneumonias of children who are afflicted with measles or pertussis and which owe their occurrence to the original disease. The fact, determined by countless investigations, that the secondary infection also plays an important part in the occurrence of this genuine influenza pneumonia and especially that in a large number of cases the streptococcus can be demonstrated ante mortem as well as post mortem, probably does not divest the generator of influenza of its original prominent position. It is predominant in the finer bronchi in the majority of cases. However, the conception of a *mixed infection* is even preserved in such cases in which it is difficult to demonstrate and in which it is overpowered by the streptococcus. Besides, cases are not absent in which the influenza bacillus singly and alone, without ally or opponent, must be regarded as the generator of the catarrhal pulmonary process.

We are all familiar with the *clinical picture* of this genuine influenza pneumonia, which, as a rule, follows the above-described primary symptoms with a marked increase of the bronchitic symptoms but which may also arise suddenly at the onset of the disease—this produces “*acute, primary influenza pneumonia*,” or “*the pneumonic form of influenza*”—or finally, it may make its appearance after the first affection has run its course. Almost invariably, provided the inflammatory process has passed beyond the bronchioles, do we observe the victim of the severe pulmonary inflammation, as markedly cyanotic or livid and struggling for air, with a relatively high fever, and, unless youth, vigor, or a robust constitution assist in a successful resistance, the well-developed signs of cardiac asthenia arise which require the utmost attention on the part of the physician. Strictly limited as these phenomena appear, they are usually accompanied with certain deviations from the ordinary picture of the acute pneumonia: The *sputum*, instead of being rusty or lemon colored, is usually of a mucoid or muco-purulent quality; conspicuously often—actually a characteristic peculiarity—it shows *recent hemorrhagic properties*, sometimes even to a marked extent being almost entirely hemorrhagic and it is then suggestive of the sputum which occurs in hemorrhagic infarct. The *fever* is irregular, remittent, sometimes intermittent; the entire course preserves the character of a protracted process, so that a definite defervescence prior to the expiration of two weeks is exceptional even in the most favorable cases. Besides the *physical signs*—another important criterion—is a decided *disproportion* in the above mentioned severe and threatening physical signs: in the greater number of cases we do not detect actual dulness nor typical bronchial breathing, but rather, fine râles which are developed and noticeable bilaterally especially in the dependent posterior portions as the most common auscultatory sign; this may be defined as an unaccented subcrepitation which is rarely interrupted by râles of a coarser quality having a purring or humming character. This additional râle persists quite obstinately for a number of days and even for weeks in different areas although with varying distinctness. This process has been very strikingly designated as the expression of the inflammation slowly advancing from lobule to lobule. However, these migra-

tory and lobular crystallizing inflammations rarely furnish very compact and diffuse consolidations, the *disseminated* form of catarrhal pneumonia rather prevails as a rule.

At this point, I must mention a special variety of genuine influenza pneumonia which I have noted more frequently at the autopsy, especially during the pandemic; this occurred more often than might be expected from textbook descriptions, which mention this condition incidentally if at all. I refer to that form which has been designated by me as "*disseminated tuberosity pneumonia*" and which belongs to the most malignant varieties among the pulmonary complications of influenza, capable of overpowering even relatively vigorous constitutions after a short illness, in fact, even at the first onslaught. In these cases we do not find ante mortem, even in those showing the severest dyspnea and air-hunger, dulness, and there is no striking alteration of the respiratory sounds; only fine crepitation, which can be heard almost over the entire chest, persisting tenaciously; this is a prominent sign. The anatomical findings correspond to this physical condition: A relatively slight involvement of the lung which, almost all over, contains air, upon the cut surface of which the palpating finger rather than the eye notes countless distinct rather hard small tuberosities, nodules eventually also, besides rather larger lobular areas of consolidation. I suspect that many authors have considered this to be a rather severe form of influenza bronchitis and were led to refer the grave dyspnea "with almost negative physical findings" to a disturbance of function of the vagus, a condition peculiar to the influenza process.

Influenza pneumonia rarely terminates by crisis. It drags along for weeks, more frequently as a subacute process, endangering the life of the patient and often terminating fatally. In such cases another conspicuous symptom usually becomes more and more prominent, viz., a *copious, pre-eminently purulent, globular sputum* which may even resemble that of advanced phthisis in which cavity formation has occurred. We were able to observe this peculiar form relatively often both in hospital and in private practice, during a period in which the actual epidemic was in the decline or had already terminated. In these cases, especially as the râles were also heard at the apices and as hectic phenomena and emaciation became more pronounced, we feared that a *tuberculous nature of the pulmonary affection* might be a secondary condition, but we were only exceptionally able to confirm this by the positive findings of the bacilli in the sputum. The detection of bacilli was impossible in the greatest majority of cases and the patients in whom an unfavorable prognosis had been made recovered entirely although only after months. In other cases the process terminated in an interstitial change, carnification and induration could not be mistaken. Thus, it is correct to a certain extent to even speak of "*chronic influenza pneumonia*." At other times the inflammatory process before resolving and before defervescence occurred, led to a fatal termination, resembling the process in phthisis florida even without the supervention of the tubercle bacillus. However, the frequency of such an outcome is not as great as in those forms which terminate in recovery. It is true in such cases we are almost always concerned with individuals who previously were not affected by pulmonary disease. In those instances in which tuberculosis plays a part, even if it be hereditary or latent,

there are good reasons for apprehension. However, we cannot enter here upon the practical important deleterious influence of grippe upon these individuals who are the subjects of pulmonary tuberculosis.

Besides, in the train of influenza, there occur *mixed pneumonias* which consist of catarrhal and fibrinous inflammations. I need not describe these complications as they do not offer peculiar clinical interest; they are occasionally designated as "*cellular-fibrinous influenza pneumonias*," nor is it necessary for me to discuss a number of other forms which often can scarcely be defined macroscopically, microscopically, or bacteriologically; they have been compiled in literature especially by the French, in actually confusing completeness.

A relatively great difference between genuine or simple bronchopneumonia and pulmonary inflammations resulting from grippe, consists in the special predisposition of the latter form to *necrosis* and *abscess formation* of the pulmonary tissue. These results are usually restricted to circumscribed areas, but they must not on this account be considered as being free from danger; but the bacteria of putrid decomposition quite frequently create violent *pulmonary gangrene* of the most serious kind. The latter, during the time of the first epidemic, repeatedly gave rise to a repulsive stench in our hospital wards, which was difficult to overcome.

Still more pronounced and practically not less important is the tendency of a pulmonary inflammation to become complicated with *pleurisy*, especially with the *fulminant* variety in which massive *exudates* form, immediately threatening the life of the patient. This justly feared exudative *influenza pleurisy*, which may occasionally arise without a preceding pneumonia, has been shown to occur in 16 per cent. of pneumonias in the previously mentioned collective investigations, a truly dreadful frequency. Some investigators even count twice as large a percentage but evidently the milder, clinically unimportant, cases were included in the latter reports. In contrast to the latter, the above mentioned forms, on account of their severity, force the physician to rapid action. Only a few cases in our hospital during the pandemic would permit of delay in puncture; the latter yielded almost exclusively, markedly cloudy, dirty, ash-yellow, sero-purulent fluid. Therefore, I have designated this variety as "*clay-water pleurisy*." I encounter this name in various text-book descriptions. Its most severe, highly dangerous forms correspond to "*pleuritis exsudativa acutissima grippalis*" of other authors. However, not only the condition of the exudate, which reminds us of clay-water, and which rapidly assumes alarming proportions, characterizes influenza pleurisy in a peculiar manner; the fibrinous contents of the latter also justify a certain separation. It manifests itself, above all, and this is not sufficiently emphasized in the literature, according to my opinion, by the practically important *great difficulty in withdrawing the effusion*. The repeated obstructions to the flow by the fibrin masses, which collect at the mouth of the trocar, or which, as flocculi obstruct its lumen, have compelled me sometimes in desperation to resort to an instrument of large calibre, to save the patient who was struggling for breath.

If, for some reason or other, necrosis of the pulmonary tissue develops, the exudate shows a *putrescent* character. These forms also distinguish them-

selves, especially in influenza, by a relative frequency, and they have, if the pus or gangrene focus is situated at the periphery, the unmistakable tendency to add a *pneumothorax* to the existing process. On the other hand, we did not very frequently observe genuine, creamy, *empyemata*, containing altered pus. It seems that a peculiar *mixed form*, the product of which was strikingly compared with wine cream, is especially prominent in some epidemics and in some localities.

The tendency to all the above named suppurative and necrotic processes of disintegration is particularly characteristic of true influenza pneumonia, and the explanation of such remarkable phenomena is scarcely difficult according to the results of the valuable anatomical investigations. It is based essentially and necessarily upon the *deficiency of fibrin* in the region of the pneumonic products of inflammation. The greater the deficiency in fibrin in the acutely infiltrated pulmonary tissue, the greater the predisposition to purulent dissolution. Naturally, the especial rôle of the pyogenic organisms must not be underrated. The streptococcus is actually found in pure culture in some thin purulent exudates.

The above are the principal complications and sequelæ that are caused by influenza in the respiratory apparatus. Their frequency is not even approximately reached by complications of the other organs. But, nevertheless, these also claim great scientific interest and frequently demand the most energetic treatment on the part of the practitioner. This applies particularly to the disturbances which are caused by grippe in our organs of *special sense*, to the *dermatoses*, and to the disorders in the region of the *urinary apparatus*, to the manifold *neuroses* and *psychoses*, and also of the organs of circulation, which may become severely affected even without the above described pulmonary complications.

Although it is not possible here to give a brief review of these complications, nevertheless, I deem it expedient to devote a few lines to the period of *convalescence* which is possessed of a peculiar character and is of especial importance. Whoever has observed and treated many influenza patients will fully agree with the view of various authors that the appearance of the period of convalescence, therefore that period which extends from the termination of the disease proper to the beginning of complete recovery, even in an uncomplicated attack, is in most cases in a remarkable disproportion to the character of the latter, especially in regard to the brief duration of the febrile period. A scrutiny of the results of the previously mentioned compilation will furnish a drastic proof of this law: More than five hundred physicians have particularly emphasized the *slow* ("dragging, protracted, tedious") course of the convalescence. The concrete statements give between two and eight weeks. The older the patient the longer the convalescence; and especially debilitated patients, neurasthenics, anemics, bronchitic patients, and those suffering from pulmonary diseases must remain quiet until they have recovered to a certain extent. Regarding the character of the disturbances, we found the following in the order of frequency: Lassitude, muscular weakness, dyspepsia, "nervous and rheumatic" pains, bronchial irritation without objective demonstrable lesion, *insomnia*, vertigo, irritable weakness of the nervous system. Finally, the protraction of convalescence became the more prominent upon

the whole, the less the patient had taken care of himself, and the more the pandemic drew to an end.

As easy as is the DIAGNOSIS of typical cases occurring during the time of epidemics of influenza, even to the tyro in medicine, so difficult may it become in atypical cases, even to investigators of great experience. The abuse which is due to superficiality and indolence has actually become proverbial. The front rank is occupied by confusion with "infectious" laryngeal and bronchial catarrhs which are accompanied with a high grade of fever and more marked general disturbance. Grave errors may be caused by typhoid fever and, which, in my opinion, is not sufficiently emphasized in the text-books, by tuberculosis. I do not refer so much to the acute miliary form, although the latter must eventually also be seriously considered, but more to the recurring catarrhs of the tuberculous patient. It occurred comparatively often that tuberculous patients, especially during my office hours, assured me that their pulmonary troubles had become aggravated in consequence of the last attack of influenza that had affected them, or that they were entirely due to the latter. This diagnosis, which was made either by the physician or by the patient himself, was confirmed, as far as actual proof was possible, only in exceptional cases.

Regarding the details, I must refer to the above description and importance of the symptoms. It is necessary especially not to determine this or that individual phenomenon but the characteristic ensemble! The bacteriological diagnosis, while conveying a welcome security in some cases, unfortunately fails us, as a rule; this has been proven in my previous statements, and it is the reason, evidently, why even the best and most recent text-books do not mention it.

Finally, it must not be forgotten, that frequently a pneumonia, pleurisy, gastro-enteritis, and other organic inflammations simulate a primary character, whereas actually, it is a question only of secondary processes in the train of influenza.

Regarding the PROGNOSIS, the erroneous opinion which was greatly disseminated at the onset of the pandemic among the laity and even among physicians, that we were dealing with an essentially harmless kind of fashionable disease, was soon corrected most forcibly by the experience which was obtained in a number of patients attacked. Whoever during the last week of 1889 cast a glance into our hospital wards was probably once for all apprised of the nature of the influenza "sport"—we have heard this frivolous word quite frequently. The new disease had actually stamped the various pavilions with the dismal character of charnel-houses and we are long since sufficiently aware that the total mortality is remarkably increased at a period of most extensive epidemics of grippe. I am not able even to admit the theory that influenza even in its severe forms does not endanger those that were previously healthy and vigorous, after I have repeatedly seen persons perish who were in the flower of youth. All experienced physicians agree that influenza represents a severe and dangerous affection for debilitated individuals, for the aged, for those previously suffering from chronic diseases or for other patients, especially if the disease selects the thoracic organs as the seat of its inflammatory complications. Influenza cannot be dreaded too much

in alcoholics, in adipose subjects, in patients with cardiac and pulmonary affections, in kyphotics and cachectics, in that it usually develops a fatal inclination to degenerate into pneumonia particularly in these diseases. According to my memory, it has reaped the greatest harvest from the group of old emphysematous and tuberculous patients. On the other hand, the oft-stated experience that neurasthenics are also greatly endangered has gradually become less distinct in mild cases; and not to create too gloomy an impression, I am thoroughly convinced that the number of those actually affected who overcome the disease is relatively great. The course of the disease under favorable circumstances is usually so brief and so smooth that those who come to sympathize must express their congratulations instead.

THERAPY

Regarding therapeutic advice, I think it is necessary to first express my conviction that there is no specific remedy for influenza. It is well known that several have been named; at one time quinine was preferred, at other times calomel, then, again, antipyrin, or a mixture of the latter with salicylic acid which was designated salipyrin. All these remedies were administered in enormous quantities to influenza patients; it is true, not without protest by critical minds whether such a proceeding was of greater advantage to the patient or, on the other hand, to the druggist and to the chemical manufacturers. The same as antipyrin in Germany, so quinine became a popular panacea in France and Russia, the drug was retailed in enormous quantities since foreign and German physicians had declared the remedy to be prophylactically of infallible effect and possessed of an absolute curative action. It is true, subsequent critical investigations brought on disagreeable disappointments; in fact experienced and unbiased clinicians came to the conclusion that patients treated with large doses of quinine were in a worse condition than those not treated at all.

Personally, we are in the fortunate position of having purposely avoided all drugs in a great number of our influenza patients; in fact, we did so in the majority of cases admitted to the hospitals during the first epidemics, and I can give positive assurance that the smooth, brief course which the milder cases took, almost without exception, compared quite favorably with that of cases which were "treated medicinally." It is imperative to know the true character of the uninfluenced forms with a natural course, to become fully aware of the deceitfulness of "*post, ergo propter.*" As a matter of fact, the preponderantly favorable course of an affection with a marked tendency to spontaneous recovery in those cases in which polypragmonists were permitted to evince their pharmacophile endeavors without control, in spite of most effective treatment, is actually surprising. [The milder cases of influenza are best managed by rest in bed without perturbing drugs; even the very lightest cases should spend one or more days in bed. In proportion as this rule is observed the number of severe and complicated cases is diminished. If one had to choose between rest in bed and good nursing without drugs and the whole pharmacopeia without the rest in bed, in all cases I should in the

interest of my patients select the former plan.—Ed.] Moreover, we cannot reconcile ourselves to the habit of administering the above mentioned remedies as “prophylactics” in the prevalence of influenza pneumonias. However, we do not mean, in expressing such an opinion, to reject the principle of prescribing *antipyretics* and *antineuralgics* absolutely. There can be no doubt, upon unbiased observation, that the above mentioned drugs, as well as phenacetin, antifebrin, citrophen, analgen, antinervin, phenocoll, aspirin, and the countless other modern preparations exert, in quite a number of cases, a favorable influence upon the subjective disturbances, especially remove the troublesome sensation of heat and ameliorate the pains. Their palliative advantage, therefore, must be admitted. However, the belief in the effect of these remedies must not be carried too far and antipyretics be exclusively employed during the entire course of an epidemic. Also beware of too powerful doses! All the above mentioned nervines are poisonous, and the injury might easily overbalance the benefit. I especially caution against the well-known formula unfortunately contained in the day-book of quite a number of physicians, $2 + 2 + 1$ grams, according to which antipyrin is prescribed to be taken every two hours in higher grades of fever. “The smaller the dose of the antipyretic which produces the antipyretic effect, the better it is,” was the statement of an acknowledged authority, especially with reference to influenza, and justly so. Single doses of 0.5 gram to, at most, 1.0 gram are actually sufficient in by far the majority of cases, as is proven by the thermometer.

Curative factors of a physical nature are employed almost as extensively, especially *heat* and *cold*. I am not able to decide which method should be preferred [The number of cases in which the trial of external cold has been of service has been, in my experience, extremely limited, and external antipyretics no longer enter into my treatment of influenza.—Ed.] Diaphoresis and a warm bath are of greater advantage in one instance, cold rubbing and an ice-bag in another. Apart from determining indications—hyperthermia, collapse, insuperable sensitiveness to cold, etc., the experiment is decisive. Those enthusiastically in favor of cold water are in a pronounced minority in the above mentioned compilation, and, to be frank, I am more in favor of warmth and rest in bed, especially in intense catarrh; if need be, with a Priessnitz pack.

In general I must advise caution against the liberal administration of *alcohol*. Excellent service as it renders in inebriates and in threatening cardiac asthenia—here we must not be sparing of strong wine and concentrated spirits of a pure quality—equally superfluous does alcohol prove under ordinary conditions. Its plentiful employment, as a rule, considerably increases the already tormenting headache, and it deprives quite a number of influenza patients of the last remnant of sleep. On the other hand, moderate doses of a better grade of wine frequently enough abolish the troublesome sensation of disease and weakness. The same favorable effect may be caused also by pure beer.

A person with a constitution that requires protection should be enjoined to remain indoors as long as possible during convalescence. An experienced practitioner insists most emphatically upon the patient, even for a week after recovery, behaving exactly as though he were still afflicted with influenza! I

am convinced that the physician with this fearless advice has avoided many relapses and many dangerous complications of the disease.

Violent pains that encroach upon the rest at night and obstinately tormenting irritation to cough always require *narcotics*. Morphin and opium head the list; codein and dionin have mostly failed, whereas the more recent *heroin* has pre-eminently rendered valuable services.

It is necessary, above all, to avoid refrigeration in winter. A late pneumonia has too often been the immediate consequence of an untimely leaving of the bed, it is, therefore, not justified to deny a causal connection between both.

Influenza pneumonia and *pleurisy* do not require any other measures than the same diseases due to other causes. If purulent or even putrid conditions of the exudates can be determined, the necessary surgical measures must not be delayed. We know of several instances in which it was possible, in spite of septic conditions, by means of the knife to cure ichorous empyematas with pneumothorax and necrosis of the lungs. If these forms occur bilaterally, they are probably always beyond hope.

INFLUENZA SINCE THE LAST PANDEMIC

BY N. ORTNER, VIENNA

HISTORICAL REVIEW

THREE epidemic diseases have challenged medical science during the last decade of the past century, and by their invasion terrified Europe and America: *Plague, cholera, and influenza*.

We all remember the terrible ravages of cholera in Hamburg in 1890, paralyzing at one stroke the life and activity of this commercial emporium. Many of us still recall how plague, the black death, invaded Portugal and England and there, although, fortunately, to a limited extent, exacted its victims. Some deaths in consequence of plague occurred but a few years ago here in Vienna, as we remember most distinctly, although the disease in these cases was due to direct infection with artificially grown pest bacilli. Finally, many of us recollect how influenza in 1889-90, descended from Asia upon Europe and, in hurricane-like flight, devastating and scorching, extended over the entire civilized world.

Plague, when it made its sudden appearance at various localities, soon became extinguished in our part of the world, thanks to a successful medical hygiene; also cholera has disappeared. Both maladies have retreated to their places of origin in Asia, without any noticeable traces of their activities among us. Does this also hold good for influenza?

We might be forced to incline to this view if we look over the history of medicine for an answer to this question and only the great pandemics are considered. These occurred, similarly to our best studied pandemic of 1889-90, at definite, constantly varying, localities, rapidly spreading over the entire world and disappearing mostly, as they had arisen, in the course of a few months. Years and decades passed by until another pandemic made its appearance. However, upon closer investigation, we shall observe that, in certain and varying localities, interspersed between these pandemics, local epidemics were very apt to manifest themselves in connection with the former, thus materially diminishing the intervals between the different occurrences of influenza. Nevertheless, longer periods of time remain—we refer to the continent of Europe—during which cases of influenza were not noted; there remain years and decades free from influenza. Therefore, if we were to follow the history of medicine, we would be justified in assuming for influenza fully analogous conditions to those of cholera and plague, diseases that descend upon us from time to time, then leave us entirely free for a certain, often quite extensive, period.

Still, according to what the last epidemics have taught us or, more correctly, by what is evinced from the time following them, such a conclusion

from analogy is erroneous; the history of medicine just in this particular is incomplete. This becomes conceivable if we consider that until 1892 no precise knowledge regarding the etiology of influenza was at hand. All that had been written concerning influenza until then had been obtained from clinical and clinico-epidemiological studies. There can be no doubt that clinical investigation is competent to determine whether a great epidemic, a pandemic, should be classified as influenza or not. However, when it is a question of the prevalence of smaller epidemics or even of sporadic cases of influenza, in such instances it is probably not always possible—in view of the clinical picture of influenza which, even in cases of fully developed disease, manifests itself in such enormous variations, in view of rudimentary forms of the affection, in view of the mildest, ambulatory cases of the malady—to make a positive diagnosis from clinical considerations alone. Moreover, it is so much more difficult to arrive at a correct decision as—future explanations shall prove this contention—there are numerous diseases in which the differentio-diagnostic separation which from genuine influenza gives rise to considerable difficulty, as there are clinical forms of influenza which, owing to their peculiarity, never attain adequate observation and appreciation within the limits of an epidemic and as, finally, influenza does not alone complicate other infectious or non-infectious maladies, thus imparting a much more ambiguous aspect to the entire clinical picture.

The Specific Organism.—That the conditions are actually as stated above has been taught by the last years, the years after the termination of the last great epidemic and pandemic; to demonstrate this has been rendered possible by *Pfeiffer's* discovery of the influenza bacillus. Who is able to tell and who may know whether the situation regarding the so-called influenza-free periods between the former epidemics and pandemics was not exactly the same or extremely similar? The history of medicine will be unable to answer this question for the knowledge of the generator of influenza was wanting.

We have been familiar with the parasite of influenza since 1892, the first great subsequent epidemic after the pandemic of 1889–90; it is the bacillus influenza discovered by Pfeiffer.

In common with by far the greatest number of the present generation of physicians, we consider this bacterium to be the undoubted, sole, and exclusive generator of grippe or influenza. We require the demonstration of its presence either *intra vitam* or at the autopsy with absolute certainty in all cases in which we establish the diagnosis of influenza, immaterial whether the latter appears to coincide with the greatest degree of probability in regard to the clinical manifestations. We consider the diagnosis of influenza to be absolutely justified only in those cases in which, by far most frequently in harmony with the clinical picture, sometimes perhaps also without the presence of influenza being regarded as probable, the specific influenza bacilli were demonstrated bacteriologically beyond doubt. When no search for influenza was made at all, or when the influenza bacillus was not found in spite of repeated attempts, we are not entitled to speak of the existence of influenza. However, the demonstration of the influenza bacilli in general (given microscopically and by culture) is not sufficient to infer from it the positive presence of an influenza affection. We require rather that they can be demonstrated in

the respective pathological products, either exclusively or at least in a considerable majority, over other accompanying pathogenic micro-organisms. We establish this postulate in harmony with all other authors who consider the influenza bacillus as the generator of influenza.

Greater difficulties are encountered in answering another question which is of eminent importance for the entire observation of influenza, I mean the question: Does the *disease* influenza actually exist in every instance in which influenza bacilli can be demonstrated even in abundant quantities? But few investigators before us have asked this question; we name in the first place Wassermann¹ who insisted: "When influenza bacilli are found, influenza is present."

But Wassermann himself restricts the validity of this statement in that he amends it with a remark that he almost never found—therefore sometimes he did—greater numbers of influenza bacilli in the sputum of certain patients in an entirely epidemic-free period. However, these are patients with residues of pneumonia or of purulent otitis media, the latter could be dated back without difficulty anamnестically to the last epidemic of influenza. Therefore, according to Wassermann, the influenza bacilli were by no means innocent parasites of the respiratory passages but they had produced severe chronic affections, causing the patients to come to the hospital.

If this represents a finding according to which influenza bacilli must be considered—and we understand Wassermann in this manner—as continuous generators of a chronic influenza affection, therefore, as specific parasites, Kruse² and Neisser³ have published cases in which influenza bacilli could be found in the sputum, or at the autopsy, without the presence *intra vitam* of signs of influenza. In the clinic of Lichtheim, Neisser examined, for influenza bacilli, the sputum of nine patients without influenza symptoms, eight times with negative results, once with a positive result in a tuberculous patient who was placed among individuals suffering from influenza. Besides, he found in a case of aortic aneurysm that came to autopsy, a pneumonic area with influenza bacilli, without manifestations of influenza being present during life. Kruse reports that he examined the sputum of a phthisical patient for months for influenza bacilli, microscopically and by culture, without success. "After the patient had died, sections of various parts of the lungs were taken at the autopsy. This gave the unexpected result that influenza bacilli grew from the pus of the large cavities and at that in pure culture; the patient did not present positive points of support for an affection by influenza during life, only loss of strength had occurred conspicuously rapidly during the last days." I believe that Finkler⁴ refers to the same case in his excellent monograph.

¹ Wassermann, Ueber differentielle Diagnostik von entzündlichen Lungenaffectionen. Deutsche med. Wochenschr., xlvii, 1893.

² Kruse, Zur Aetiologie und Diagnose der Influenza. Deutsche med. Wochenschr., xxiv, 1894.

³ Neisser, quoted from Beck: Influenza in Lubarsch-Ostertag's Ergebnissen der allg. Aetiologie der Menschen und Thierkrankheiten. Wiesbaden, Bergmann, 1896.

⁴ Finkler, Infectionen der Lunge durch Streptokokken und Influenzabacillen. Bonn, Cohen, 1895.

Kretz,¹ by reason of very exhaustive bacteriological examinations, arrived at the clearly defined conclusion that, "similarly as in other infectious diseases, the finding of bacilli persists considerably longer than the symptoms of the disease and that there exist also healthy persons who may be the carriers of influenza, at least subsequent to an acute attack." Upon careful examination, Kretz was able to find isolated bacilli in absolutely healthy individuals without any morbid phenomena whatever—apart from a slight smoker's catarrh—even several months after an acute attack of influenza. Among 47 carriers of influenza bacilli, he noted only 12 who were considered by clinicians with more or less probability to be affected with influenza, whereas the other 35 cases could not be determined, "as they harbored influenza bacilli without the typical affection." Kretz quotes, as a very conspicuous instance, a case history which, owing to its importance, shall be briefly outlined: "This man who suffered from hypertrophy of the heart with engorgement, owing to chronic Bright's disease, in June, showed isolated influenza bacilli in the sputum without an acute affection having preceded or without symptoms of an intense bronchitis having existed. The patient succumbed after five weeks without the occurrence of influenza symptoms; at the autopsy—besides the fatal renal affection—large quantities of influenza bacilli could be cultivated from the bronchial mucus, and the mucous membrane at the same time was thin and pale; a classical example of the possibility of a finding of influenza bacilli without an affection of influenza of the host."

Finally Perez² expresses this opinion in contrast to Rosenthal³ who, as we also believe, incorrectly, and without any tenable foundation, regards the influenza bacillus or cocci bacillus hemophilicus as a simple saprophyte, depriving it of any specificity whatever, in that he states: "It may not be astonishing that the influenza bacillus, although it is not an ordinary saprophyte of the lungs, under certain conditions may be present in the respiratory organs in a certain physiological condition of accommodation, most frequently in such individuals who previously have been affected by an attack of influenza." We also concur in this view if we consider, which is also pointed out by Perez, that "also other, much more virulent, bacteria than the bacillus Pfeiffer, such as the tubercle bacillus, the diphtheria bacillus, the pneumococcus, may be present in various affections as well as in normal individuals upon the mucous membranes and may even enter from the latter into the lymph vessels without, however, causing any of the phenomena which are peculiar to the diseases produced by them." To be logical, Rosenthal should also deny the specificity of the tubercle bacillus, of the diphtheria bacillus, etc. Logically, the typhoid bacillus also would become a simple saprophyte if we would consider cases in which typhoid bacilli can be demonstrated in the urine even weeks and months after the typhoid affection has run its course without absolute recovery of the individual. I was able to demonstrate such a case during the present winter, in which, two months after

¹ Kretz, *Influenza-Beobachtungen im Jahre 1897*. Wiener klin. Wochenschr., xl, 1897.

² Perez, *Die Influenza in chirurgischer Beziehung*. Deutsche Zeitschr. f. Chirurgie, Bd. lix, 1901.

³ Georges Rosenthal, *Recherches sur quelques cas de Broncho-Pneumonie aiguë*. Thèse de Paris, Steinheil, 1900.

the typhoid affection, the typhoid bacillus was demonstrable in the urine in pure culture, and in which it appeared in such quantities that bacteriuria was assumed even after microscopical inspection.

I was also able to present several other cases, phthisical patients, in whom we were able to demonstrate intra vitam abundant influenza bacilli in the sputum, besides tubercle bacilli, both by microscopical examination and by culture, without being justified from the clinical findings in speaking of a demonstrable influenza in a tuberculous individual. We also explained these cases in such a manner that the influenza bacilli were dormant in a cavity without playing, for the time being, a rôle of significance or without being clinically noticeable.

Accordingly, by reason of our own experience and by the observations of others, we answer the above mentioned third question in this manner, that not always when influenza bacilli are demonstrable, even in abundant numbers and in pure culture, is the affection influenza present. There are cases in which, in spite of influenza bacilli being present in the sputum, no influenza is demonstrable, in which the bacilli therefore, analogous to many other pathogenic bacteria, remain in a non-aggressive condition.

These view-points as developed above shall dominate our conception of influenza. They are briefly condensed in the statement: No influenza without the presence of influenza bacilli. Influenza is not necessarily present in every instance in which influenza bacilli are demonstrable even in abundant numbers. Whenever the clinical picture does not allow the assumption of influenza in any form we deny the presence of this disease even when influenza bacilli can be demonstrated bacteriologically. They are healthy carriers of influenza (Kretz). Numerous analogous cases from bacteriology concerning other pathogenic micro-organisms tend to reinforce this postulate.

Thus equipped, we may now enter upon the answer to our question proper: What do we know regarding influenza since the last pandemic?

By reason of our own observations and those of others, we may lay down the principle that influenza has never become fully extinct from the last pandemic, or even epidemic, up to the present time, at least it has become an endemic disease in our localities, it is found at any season and especially predominates each winter and each spring. [In this respect influenza resembles cerebro-spinal fever, which often persists as an endemic or sporadic affection in localities in which it made its first appearance in the epidemic form.—Ed.]

More numerous cases of influenza can be determined every year at this period; the first occurrence of the same usually takes place in the month of November, increasing till the New Year, reaching the acme during February and March, then declining again. Sometimes the cases accumulate in such a manner as to form small epidemics, at other times they make their appearance isolatedly at different places (sporadic cases), and the latter may also be observed at any other season of the year. Leichtenstern's¹ hope which he expressed in 1896, that "the seven-year period of influenza which has been

¹ *Leichtenstern*, Influenza in Nothnagel's Special Pathologie und Therapie, Wien, Hölder, 1896.

determined is nearing its end, the germs spread by the pandemic of 1889-90 are gradually dying and influenza vera will disappear; several decades will probably pass again until a renewed mighty pandemic will disseminate, over the entire earth, the germs which will be active for many years," has not up to the present time been realized. Influenza has become a permanent guest with us, the presence of which must be taken into consideration to-day as much as a decade ago.

This has been taught, above all, by the numerous anatomico-bacteriological investigations made by the different authors since 1892. The number of clinical observations is of minor consideration in view of these researches although, naturally, it is of no less importance to the clinician than to the pathologist to have an exact knowledge of the continuous existence of influenza.

Influenza manifests itself in an entirely different form clinically since the pandemic of 1889-90, or even in the subsequent epidemic of 1891 and 1892, immaterial whether it occurs, as stated above, in small epidemics or sporadically.

VARIETIES OF INFLUENZA

Primarily we must distinguish two sub-groups, namely, one in which only the end products of an influenza infection which has run its course some time previously (months and years) and a second group in which an attack of influenza must be assumed as *existing at the time*.

Regarding the first group, I should like to be brief, as, in spite of the great amount of clinical material which has been gathered, it only brings to our remembrance facts with which we are familiar from the pandemic of 1889 and 1890 and the succeeding years. It is only necessary to call attention to the fact that diseases of the heart, at one time those of the heart muscle, at another time those of the endocardium, still present themselves to us to-day as post-influenza affections, how inflammatory diseases of the blood vessels (thrombo-phlebitis) in their terminal stage of venous thrombosis, or chronic endarteritis, or even arteriosclerosis may be referred to an influenza which has run its course some years previously; how inflammatory diseases of the kidney which still show themselves at the present time by their chronic course may be brought into causal relation with recovery from acute influenza; how chronic otitis in its terminal stage may be proven to be due to an attack some time past; how a great number of surgical diseases¹ may be shown to be due to a long past grippe; but especially how various chronic pulmonary maladies are met with at the present time which are the sequels of an attack of influenza dating back many years. Apart from pulmonary abscess, pulmonary gangrene and old pleurisies, I must lay special emphasis in this connection upon a peculiar variety of influenza pneumonia which even during the time of the first influenza pandemic was observed by careful physicians and which since that time has been confirmed by numerous authors. I refer to the frequent transition of those areas of the lung affected by influenza which terminate in

¹ Compare *Perez, loc. cit.*, and *Franke* (Ueber einige chirurgisch wichtige Complicationen und Nachkrankheiten der Influenza. *Langenbeck's Archiv*, 1899, Bd. lix), who, as they establish a diagnosis of influenza without a bacteriological investigation, refer many affections to this disease which is perhaps not justified.

pulmonary induration. Kundrat,¹ Weichselbaum,² and Pfeiffer³ have described the pathology, Drasche,⁴ but especially Fränkel,⁵ have described the clinical appearance and called special attention to the condition. It should also be mentioned that they did not determine these facts upon the basis of cases which were taken from the severe epidemics, but from observations of patients in the subsequent years after the affection had passed. A chronic indurative pneumonia which may implicate an entire lobe of the lung or only a part must even to-day remind us of the possibility that its origin was due to a recovery from an influenza pneumonia long past and from which it obtained its lobar or lobular character. Bronchiectasis may be the result of a past acute influenza, a fact to which Romberg⁶ called attention; he said: "Not rarely in areas of the lung attacked by influenza does abscess and gangrene occur, or in portions that have undergone indurative changes is bronchiectasis noted." I shall take the opportunity in the course of the description of influenza (as the affection is met with at the present time) to give the case history of a typical attack, and these facts must concern us to a marked extent in considering the connection between influenza and tuberculosis. In this connection I shall also report a case in which a chronic pulmonary induration occurred in a tuberculous individual, which was not the expression of the tubercular process but that of the concomitant influenza, and shall refer to the scholarly work of Finkler who years ago reported quite analogous observations.

Accordingly, influenza, even to-day in this first sub-group, which has been briefly sketched by me, in which manifold pathological processes show themselves in nearly all of the internal organs, which are not recent, in which the source of production may be referred to an influenza from which recovery has taken place some time previously, manifests itself.

In contrast to this first sub-group, a second is to be considered, which is the theme of the present article.

This group is to include all cases of influenza which have occurred since the last pandemic and the greater epidemic of 1891 and 1892, also those cases occurring in small endemics and even in sporadic forms. As most of these cases are subject to the same laws both in their clinical appearance and course as those which I studied with especial attention a year ago and those which may be gathered from a review of the literature, I shall base the description of these cases upon my own investigations.

One fact becomes conspicuous at once: By far the greatest number of cases may be placed in that subdivision which we have been accustomed to call the *respiratory form* of influenza, since the pandemic of 1889 and 1890.

¹ Kundrat, Ueber anatomische Befunde während der Influenza-Epidemie. Wiener klin. Wochenschr., viii, 1890.

² Weichselbaum, Beitrag zur Aetiologie und pathologischen Anatomie der Influenza. Wiener klin. Wochenschr., xxxii-xxxiii, 1892.

³ Pfeiffer, Die Aetiologie der Influenza. Zeitschr. f. Hygiene u. Infect.-Krankh., Bd. xiii, 1893.

⁴ Drasche, Influenza. Wiener med. Wochenschr., 6 u. ff., 1890.

⁵ Fränkel, Klinische und anatomische Mittheilungen über indurative Lungenentzündung. Deutsche med. Wochenschr., 10 u. ff., 1895.

⁶ Romberg, Influenza in Mering's Lehrbuch d. inneren Medicin. Jena, Fischer, 1901.

It is pre-eminently the respiratory tract, from the nose to the alveoli of the lung which shows pathological changes, whereas the other varieties, the gastrointestinal and the nervous types of influenza (the hemorrhagic form of influenza according to Maragliano ¹ I shall omit) are only of secondary consideration. It is true the observations pertaining to the latter varieties, in spite of the fact that they are fewer in number, are clinically no less important. In this connection I must call attention to cases of purulent meningitis which were described as influenza meningitis and occurred after the great epidemics. Pfuhl ² in 1896 published two such cases, Fränkel ² in 1898 and also Hegerstedt ³ found the influenza bacillus as the pathogenic agent in a case of purulent meningitis. Analogous observations, each author reporting one case, ⁴ have been reported in 1901. In one of these cases, in the fluid obtained by lumbar puncture, numerous polynuclear leukocytes and pure cultures of influenza bacilli were obtained. The brain substance itself, similar to the meninges, may be attacked by influenza bacilli by way of metastatic embolic processes, a fact the knowledge of which we owe to the bacteriological studies of Pfuhl ⁵ and Nauwerk. ⁶ Owing to these investigations it has been determined in an unquestionable manner that a multiple acute hemorrhagic encephalitis occurs, produced exclusively by influenza bacilli.

Similar to this implication of the brain, in individual cases the circulatory apparatus was shown to be affected to a marked extent by the bacillus of influenza. I mention Grassberger's ⁷ observation, who in 1897 found besides streptococci, influenza bacilli in a pericardial exudate, and also Jehle's ⁸ very interesting observations. This latter author demonstrated in the "Society of Physicians" in Vienna, two cases of bacterial endocarditis of the aortic valves in one of which influenza bacilli were found in pure culture, and in the other case they were detected in combination with staphylococci, in one of the cases a severe influenza bronchitis complicated the condition, in the other case no complications were present; besides in this case numerous influenza bacilli could be cultivated from an old tubercular focus in the apex of the left lung. "Even though it is possible that influenza bacilli may be regarded as the secondary pathogenic agents of endocarditis, this is still unlikely as they are found in one case in pure culture, and the early destruction of other micro-organisms is unlikely." With these words Jehle closed his demonstration.

A similar interesting observation was lately published by Schlagenhauser ⁹

¹ Maragliano, L'Influenza dal punto di vista della clinica, della pathologia e della therapia. La Riforma medica, 14 Jahrg., 1898.

² Pfuhl und Fränkel quoted from Jehle: Zwei Fälle von Influenza-Endocarditis. Wiener klin. Wochenschr., li, 1899. Centralbl. f. Grenz. d. Med. u. Chir., S. 835, 1901.

³ Hegerstedt, Petersburger med. Wochenschr., 1895. Also quoted from Lubarsch-Ostertag's Ergebnisse, etc., 1900.

⁴ Trailescu, Spitalul, 1901, rep. in Münchener med. Wochenschr., iii, 1902.

⁵ Pfuhl, Deutsche med. Wochenschr., 1895.

⁶ Nauwerk, Deutsche med. Wochenschr., 1895.

⁷ Grassberger, quoted from Jehle: Wiener klin. Wochenschr., li, 1899.

⁸ Jehle, Zwei Fälle von Influenza-Endokarditis. Wiener klin. Wochenschr., li, S. 1297, 1899.

⁹ Schlagenhauser, Ein Fall von Influenza-Endokarditis der Aortenklappen und des offenen Ductus Botalli. Zeitschr. f. Heilkunde, Bd. xii (N. F., Bd. ii), 1901. Abtheilung f. patholog. Anatomie.

who reported a case of relapsing endocarditis of the aortic valves and of the ductus Botalli, in which influenza bacilli besides other bacteria could be determined microscopically and in culture from the endocardial vegetations. These bacilli must be looked upon with the greatest probability as the pathogenic agents of the inflammatory infection. Schlagenhauser also quotes a case of Austin, mentioned by Schott, who demonstrated influenza bacilli microscopically in the vegetation from the valves in a case of endocarditis; however, culture experiments were not successful.

At any rate these cases prove that in acute meningitis, in acute processes of the endocardium and pericardium, even though rarely, we may find that they are due to infection by influenza and for this reason the influenza must be kept in mind in our etiologico-diagnostic considerations. Paltauf's¹ studies of influenza which were published in 1899 deserve special mention; he succeeded in finding influenza bacilli in the kidney and in the bladder and several times also in the spleen, and Albrecht and Ghon² refer to the possibility that Kretz, in a case of pyelitis, was probably dealing with the bacillus of influenza as the cause of the affection.

But apart from these rare cases, we find influenza as it exists to-day and as it has been noted since the last pandemic, to assume the respiratory type in an enormous majority of the cases. In view of this, I believe that we may subdivide the cases of endemic influenza, according to my own observations, into several sub-varieties. The *first variety* includes all cases of *acute influenza*, the *second variety* all cases of *chronic influenza*, both existing as exclusive or (in regard to chronic influenza) at least as the dominating affection; the *third subdivision* includes all cases in which *influenza occurs as a complication of other pre-existing or coexisting acute or chronic morbid processes*.

As the result of this arrangement, we shall first discuss among the varieties of endemic influenza:

ACUTE INFLUENZA

A single brief illustration is sufficient: A physician, previously healthy, with the exception of attacks of gall-stone colic, which appeared for the last time two years previously, was taken ill after having treated a patient suffering from influenza pneumonia. The symptoms in the physician appeared upon the eleventh of March, manifesting themselves by chills, coryza, cough, intense headache, general lassitude, pain in the limbs.

The objective findings show: A temperature rise to 102.2° F. Acute laryngotracheitis and a right-sided bronchitis, with muco-purulent expectoration, the nose dry, completely clogged, total anosmia and ageusia. The patient is tortured by intense neuralgic pains which were first limited to the region of the first and second branch of the fifth nerve but later also the third trigeminus branch gave rise to pain of a boring and lancinating character, which penetrated from the hard palate to the top of the skull and in the

¹ Paltauf, Wiener klin. Wochenschr., xxi, S. 576, 1899.

² Albrecht und Ghon, Ein Beitrag zur Kenntniss der Morphologie und Pathologie des Influenza-Bacillus. Zeitschr. f. Heilkunde, Bd. xxii (N. F., Bd. ii), 1901. Abtheilung f. pathol. Anatomie.

stage of amelioration permitted the recognition of how the frontal sinuses, the ethmoidal cells, and the sphenoidal sinuses, gradually evacuated their contents. "These neuralgias were so severe that it is easy to understand that many patients are driven to despair and even suicidal intentions by these paroxysms of pain." After a febrile period lasting three days, the fever disappeared and there was a tendency to sweat, with a continued high-graded disturbance of the general condition. The secretion from the nose and the sputum became purulent and contained influenza bacilli in pure culture in large quantities. Only after nine days from the onset of the affection did the severe right-sided trigeminal neuralgia cease and two days later, finally, the neuralgic implication of the left side also disappeared. The general lassitude still persisted until after a residence of three days in the mountains, increase of appetite and return of strength were noted, a cessation of the purulent secretion from the nose and bronchi ceased, and soon complete euphoria took place.

Such cases of typical acute pneumonia in previously healthy individuals, which were noted in incalculable numbers during the pandemic of 1889-90, have been relatively scarce since that period and are even relatively infrequent now. I have lately, i. e., in the period from November, 1901, until the end of May, 1902, seen but six cases of pure acute influenza. The clinical picture corresponds completely to the symptom complex of the individual affection during the great pandemic and, as in the greatest majority of cases at that time the respiratory type was predominant, this is also the case to-day with the sporadic cases of this subdivision, that is in those cases which occur yearly between epidemics and endemics.

Lindenthal¹ has especially called attention to their appearance, he being the first to use the expression "sporadic influenza" but he was preceded by Richter,² both observers having determined the affection upon the basis of anatomico-bacteriological investigation and the second named author quite properly maintains that a bacteriologic investigation of the cases of bronchitis and pneumonia which occur year in and year out would lead to the decision that some of these affections were influenza. In view of this fact, influenza must be grouped among our endemic diseases and "the outbreak of an epidemic of influenza will not surprise us any more than the epidemic appearance of diphtheria or variola which are endemic here."

As far as I know, Finkler³ in his very valuable monograph was the first to expressly define sporadic influenza upon the basis of clinical observations. He described individual characteristic cases which demonstrated the condition. Since that time probably all clinicians are convinced of the existence of such cases by their own observations. As has been mentioned, these cases do not show themselves clinically in a different manner from individual cases of epidemic acute influenza. The case of the physician just described by me will serve as a model to recall the clinical symptoms of this form. The severe phenomena on the part of the nose, the symptoms on the part of the cranial cavities, the severe and tenacious trigeminal neuralgias are the expression of

¹ *Lindenthal*, Ueber die sporadische Influenza. Wiener klin. Wochenschr., xv, 1897.

² *Richter*, Zur Aetiologie der Influenza. Wiener klin. Wochenschr., xxix-xxx, 1894.

³ *Finkler*, loc. cit.

an inflammatory implication of the cavities of the nose, then the febrile and general toxic symptoms (prostration, muscular pains, pains in the small of the back), the relatively protracted convalescence, the tendency to sweat during the same, the continued existence of neuralgias during this period, and finally complete recovery.

Our case shows a certain special interest in so far that in the secretions from the nose profuse quantities of influenza bacilli could be obtained in pure culture. This proof especially deserves observation; for the pandemic of 1889-'90, but particularly the following epidemics confirmed the finding of Pfeiffer's bacillus; but the cases did not always show such a typical clinical picture, cases of an apparent simple coryza, in which scarcely a noteworthy implication of the organism, with hardly a disturbance of health, may be due to influenza. The bacteriological findings in the nasal secretion is alone determining, a fact to which Pfeiffer¹ particularly called attention. Störk² expresses this fact, for he says that even in walking cases he was able to determine the presence of influenza bacilli in the nasal mucus. This bacteriologic investigation is all the more necessary as there are many other affections, above all, simple catarrhal processes due to refrigeration, which resemble these mild and sporadic cases of influenza so completely in a clinical respect, without having the slightest in common with them. To separate one from the other and not to fall into the habit of using the word grippe within the meaning of a true infectious disease produced by Pfeiffer's bacillus, for other conditions, a bacteriologic examination is necessary. I desire to use Pfeiffer's remark, probably because it is not so familiar to clinicians in general that, according to his investigations of the nasal secretion of ordinary coryza, he has found that this secretion shows but very few bacteria, in fact being almost sterile.

Acute sporadic influenza, as may be expected, runs a course not only under the clinical picture just described in which the infection relates particularly to the upper air passages (nose and accessory cavities) and the signs of a general intoxication, but more frequently an implication of the deeper respiratory passages, namely, those of the trachea and of the bronchi. Just these cases are met with year in and year out and they may serve as a model of sporadic acute influenza, but they are not always clothed with all the peculiarities of the affection as is represented by the large number of cases occurring in pandemics and epidemics. In close analogy, however, to these cases, sporadic influenza may appear in the form of a classical influenza pneumonia, with, or without, bronchitis. The affection may show all those complications which occur in such great numbers in epidemic influenza.

A case in point is that of a man, aged fifty-eight, who was admitted to my ward on March 15th, with symptoms of an acute rhinotracheo bronchitis, temperature 101.3° F., with marked headache, trigeminal neuralgia, pains along the spinal column, and general prostration. The eye showed a keratitis nummularis which the eye specialist, Dr. Müller, declared to be a classical influenza affection, unfortunately, particularly in regard to this opinion, only nine days after the onset of this affection, the secretions from the conjunctiva

¹ Pfeiffer, *loc. cit.*

² Störk, *Die Erkrankungen der Nase, des Rachens und des Kehlkopfes in Nothnagel's Spec. Pathologie und Therapie*, Bd. xiii, Hölder, 1895.

were examined bacteriologically—in the purulent nummular sputum for the first time profuse numbers of influenza bacilli besides staphylococci were demonstrated, upon another occasion moderate numbers of influenza bacilli besides staphylococci were present. Influenza bacilli could no longer be shown in pure culture, only the bacterium xerosis could be obtained. The patient was discharged cured, and did not show any signs of disease on the part of the eyes or of the respiratory tract.

I have notes of three other cases of influenza which occurred during the last six months; of the three cases, the disease began in two with a well developed chill, once with chilliness; in each of the cases this was followed with fever; there occurred headache, lassitude, cough, in one of the cases marked hoarseness, marked lachrymation and coryza with secretion from the nose, in one of the cases gastric colic with vomiting, in one of the patients well developed muscular pains especially in the back and the calves. The patients were admitted to the hospital after the affection had lasted eight, ten, fourteen days respectively.

In the first case the objective finding showed a rise of temperature to 99.3° F., the second case during the first three days a remittent intermittent temperature up to 104° F. was present, in the third case throughout the three days in the hospital a remittent temperature up to 104.2° F. In the first patient there was a diffused dry bronchitis with but sparse, muco-purulent, greenish globular sputum in which large amounts of influenza bacilli could be demonstrated (at first in connection with the diplococcus and staphylococcus albus, later also with the streptococcus). After a stay of eleven days in the hospital the patient was discharged cured. The second case showed an exclusively left-sided bronchitis which was partly of the dry variety, with constant sparse muco-purulent expectoration in which quantities of influenza bacilli were present (the sputum also contained Friedländer bacilli). The influenza bacilli (and also the Friedländer bacilli) disappeared from the sputum two weeks after the admission of the patient to the hospital, whereas the bronchitis, although it lessened, had not entirely ceased upon the day that the patient left the hospital.

It was possible to demonstrate in the third case a diffused, principally dry catarrhal process with a particularly abundant muco-purulent expectoration, which for the time was intermingled with globules of blood, in which abundant amounts of influenza bacilli could be isolated; at first there were some few streptococci and the staphylococcus albus present; later, two weeks after the second examination of the sputum, i. e., fifty-two days after the onset of the affection, the influenza bacilli had completely disappeared from the sputum and every trace of the bronchitis had vanished. This patient showed great tendency to profuse perspiration during convalescence. He recovered entirely.

If, after the above brief outline, we now ask whether these three cases of acute sporadic influenza—in the third case the influenza bacilli could be demonstrated for at least twenty-eight days—were characterized by any clinical peculiarities which might suggest the diagnosis of such an affection, we are compelled to answer in the negative. They did not present anything else than the picture of a febrile bronchitis, there being no conspicuous involvement of the organism nor painfulness at the points of exit of the trigeminus,

signs which, in my opinion, should not be underrated in the diagnosis of influenza, namely, the sensitiveness of the accessory cavities of the nose to pressure—only in one of these cases was this symptom present to a slight extent—without a peculiar condition of the sputum. We must particularly emphasize this latter factor, as Finkler,¹ in his excellent monograph, to which we have repeatedly referred, lays special stress upon the fact that “the influenza bacilli very rapidly produce a purulent condition in the secretion of the bronchi, so that this purulent condition in a rapidly arising bronchitis renders the assumption very probable that an influenza infection is present,” unless a streptococcus infection can be proven.

We quite willingly admit the correctness of Finkler's statement that purulent, nummular sputum occurs quite frequently in acute influenza; however, when the latter is absent, and when a watery-mucus, muco-purulent or, as in the third case as mentioned above, simultaneously a purulent and a hemorrhagic sputum exists, this fact is by no means against the presence of influenza, and this deserves special emphasis.

Finally, the last case of sporadic influenza which quite recently came under our observation, was that of a young girl, L. P., fifteen years of age, who was admitted to the hospital on May 5, 1902. She was at first affected by a lobular pneumonia of the right upper lobe (fever up to 103.6° F. which two days later only amounted to 99.3° F.), after two days of observation it almost entirely disappeared.

Another rise of temperature to 100.8° F. occurred on the third day, with the formation of a new lobular pneumonic focus in the left lower lobe adjoining the vertebral column, which still persisted at the date of the report (May 31), with changeable manifestations of resolution and normal temperature. During the first pneumonia in the right upper lobe the sputum appeared as a typical sputum croceum, in the second pneumonia it was only muco-purulent. The first examination revealed numerous colonies of influenza bacilli, sparse colonies of streptococci and staphylococci; an examination undertaken after the occurrence of the second lobular-pneumonic focus showed plentiful colonies of influenza bacilli and also of streptococci.

Above all, the case was characterized as influenza pneumonia by the appearance of a lobular pneumonic area, at a period at which a preceding focus at another point had just terminated by resolution, and also by the abnormally slow resolution of the second lobular pneumonic area (twenty-three days up to the time of the report). The manner in which it deviated from the rule was by the presence of the typical sputum croceum containing numerous influenza bacilli and only sparse streptococci and staphylococci, this deserving particular attention. The case proves that an influenza pneumonia may be present with entirely characteristic sputum croceum, and it suggests the view which was already maintained by Fränkel² that the influenza bacilli are also able, although rarely, to produce rubiginous sputum.

All of the above explanations have taught us the important postulate: Whenever we encounter an acute, more or less febrile, bronchitis, we are

¹ Finkler, *loc. cit.*

² Fränkel, Ueber einige Complicationen und Ausgänge der Influenza. Berliner klin. Wochenschr., xv und xvi, 1897.

compelled in each instance to examine the sputum for influenza bacilli; for, outside of the pandemics and the epidemics, there exist sporadic cases of acute influenza which the clinician must appreciate in particular because of the danger of a possible propagation of the disease.¹

As will be noted, the few cases which I quoted as examples of acute sporadic influenza belong to the catarrhal-respiratory type of the disease. I did not personally observe or find reported in literature, a single case of the intestinal type, and I found only a few isolated cases in which the typhoid type of the affection was unquestionably prominent. To this I shall refer later on.

The review of all observations which have been reported regarding sporadic influenza occurring in individuals, otherwise healthy, proves, under all circumstances, that the *catarrhal-respiratory type* of the affection predominates quite as much in this form as in epidemic influenza; this is quite obvious, for influenza is an infectious disease in which the primary port of entrance of the infection, in by far the majority of cases, must be looked for in the respiratory tract. From here, either by entrance of the bacteria into the blood or by remote toxic action, morbid phenomena may become manifest, which are situated at a distance from the original focus. The respiratory tract might not be the only point of invasion, for exceptionally the influenza bacillus may also enter through the digestive canal, although the majority of cases of the intestinal type must also be explained as of toxic origin. It is quite as probable that the influenza bacillus may enter into the organism primarily through the skin. It was to this fact in particular that an observation of Albrecht and Ghon² called attention—of pandemic periods separated from epidemic periods.

If sporadic acute influenza presents the same symptom-complex as acute epidemic influenza; if it may be accompanied with the same complications and be followed by the same sequelæ as the latter; if, accordingly, the prognosis of both forms of manifestation does not differ, we must in many directions express ourselves differently regarding another form of influenza which, during the pandemics and epidemics, has only been partially observed, that of CHRONIC SPORADIC INFLUENZA.

If we speak of influenza we are generally inclined to think of the above-described acute form of the disease. Still we know, since we are familiar with the influenza bacillus, that the latter is able not only to cause an acute specific infectious disease, acute influenza, but also that it may persist for a long period, for many months, in the human organism.

Pfeiffer³ himself clearly expressed this fact when he wrote: "Up to the present time, it appears that it has been entirely overlooked that there exist, besides the typical forms of influenza with an acute course, chronic affections of grippe which may be protracted for weeks and months. These chronic forms, according to my experience, occur principally in individuals whose lungs, even before the infection by influenza, represented a point of inferior resistance. It is mostly a question of tuberculous persons in an advanced

¹ Compare also *Jundell* (Hygiea, November and December, 1891); quoted from *Semaine médicale*, 1902, No. 21.

² *Albrecht und Ghon, loc. cit.*

³ *Pfeiffer, loc. cit.*

stage in which the formation of cavities has taken place” This statement of Pfeiffer has been confirmed by many other authors, viz., the presence of a chronic influenza affection in tuberculous individuals. However, this is not the question in our case, but we desire, above all, to describe as chronic influenza those forms, of influenza infection, in which, without tuberculous affection, or without another conspicuous affection of the lungs, influenza persists for months and occupies an independent or, at least, a dominating position.

CHRONIC INFLUENZA

We mean to establish two different types of chronic influenza, the first is that type in which influenza in its usual form arises as an acute infectious disease, at first takes its accustomed course but does not terminate within the period of twenty-four days which is generally assumed as peculiar to a so-called acute disease, but in which weeks and months have passed before the affection has come to an end. Such cases have also occurred in considerable numbers during pandemics and endemics, sometimes taking their course only in the form of chronic influenza bronchitides, at other times as chronic influenza pneumonias.¹ Finkler,² as well as myself, has repeatedly seen patients who acquired an influenza with acute onset with the more or less typical picture of an intoxication and with the local symptoms of febrile bronchitis. The febrile rise of temperature had passed within a few days but the bronchitic phenomena persisted in their intensity, in the abundance of the sputum, continually changing in intervals of days or weeks until their final disappearance. Both at the onset and in the further course of the disease, numerous influenza bacilli could be demonstrated in the sputum, either in pure culture or in association with other varieties of bacteria, over which they predominated in numbers (streptococcus, staphylococcus, and diplococcus).

What is true of chronic influenza bronchitis is also true of chronic influenza pneumonia. As frequently as the latter terminates in resolution within a few days, naturally to occur in another pulmonary area, there are besides cases of classic chronic influenza pneumonia which persist for months. These are the cases which—Wassermann³ in an excellent manner first called attention to them—are most apt to lead to a confusion with tuberculosis if the pneumonia occupies one or both upper lobes of the lungs. The conspicuous phenomena of pulmonary infiltration, dulness, and bronchial respiration, may persist for months in such cases; the temperature of the body, which at the

¹ *Filatoff* (Protracted and Chronic Form of Influenza. *Archiv für Kinderheilkunde*, xxvii, 1899) also describes cases of chronic influenza lasting several months, in which he emphasizes particularly catarrhs of respiratory organs, which are said to run their course under the picture of a remittent or intermittent fever mostly of moderate height only with general symptoms and with a tendency to perspiration. We do not attempt to classify these cases as influenza with certainty, as *Filatoff* unfortunately omitted the bacteriological examination of the nasal secretion which was almost always at his disposal. Naturally, we do not mean to deny the possibility of such cases; in fact, we consider them probable, but not proven.

² *Finkler*, *loc. cit.*

³ *Wassermann*, *loc. cit.*, and *Influenza in Ebstein-Schwalbe's Handbuch der prakt. Med.*, Stuttgart, Enke, 1901.

onset is raised, may become normal during the further course of the disease, or there may only be slight increases of temperature with a tendency to perspiration, the patient becoming greatly debilitated. It is not astonishing then if we continuously fear a tuberculous infection or a transition of the original influenza infection into a secondary tuberculous infection of the lungs. I shall never forget a case in my private practice in which such an influenza infiltration of the upper lobe persisted for about six months, finally terminating, clinically at least, in complete recovery. The sputum contained pure cultures of influenza bacilli mostly, rarely accompanied with other bacteria (streptococci, diplococci). In such cases it is possible to obtain certainty, i. e., the desired proof, only by an examination of the sputum, possibly only by a trial injection of the smallest ($\frac{1}{10}$ mg.) quantities of tuberculin.

The above brief sketches of analogous personal observations may suffice for they do not offer anything new and are only repetitions from the last epidemic of influenza.

It is different, however, with *the second type of chronic sporadic influenza* to which, so far as I am able to judge from a perusal of the literature, sufficient attention has not been paid. I refer to cases in which the connection of chronic influenza with an acute influenza infection is not demonstrable at all, in which influenza has never attacked the patient in an acute manner but has insidiously descended upon the latter; in such cases chronic influenza occurs, from the onset of the disease, as an exquisitely chronic, a primordial, form of manifestation of the infectious disease. Besides, there exist exquisitely *chronic rhino-tracheo-bronchitides or tracheo-bronchitides which run their course entirely without fever and which must be considered as chronic influenza*.

I am justified in establishing this postulate, as I believe, by my own observations, which I am compelled to report more exhaustively as they represent a form of influenza which is but little, or not at all, known. As an example, I shall detail the case of a patient, J. Z., sixty-seven years old, a private official admitted to the hospital October 28, 1901.

HISTORY.—Father died of inflammation of the lungs, mother of typhoid fever. The patient stated that he had had a cough from youth. When in the army, forty-seven years previously, he was afflicted with right-sided pneumonia, two years later with dysentery; subsequently he acquired syphilis. Syphilitic ulcers in the pharynx and larynx did not appear until sixteen years later; antisyphilitic treatment effected a cure. In 1889, during the epidemic of influenza, patient became affected with influenza, in Budapest, this lasting from four to five days, and which was of such a mild degree that he was not prevented from attending to his business. Afterwards he was well until about nine years ago, when he was attacked, as well as every following year, by cough with expectoration. That year, however, he was compelled, owing to stiffness of the neck, burning sensation in the chest, and loss of appetite, loss of weight to 48 kilograms, to apply for admission to the hospital.

An inunction cure, with electrical treatment, caused material improvement. However, from this time on the patient coughed without interruption; the sputum was always of a gray mucus character. Up to two months ago the patient was able to follow his occupation, but as then very marked, painful, nightly spasms of the calves of the legs made their appearance, lasting from one to two hours, and also, upon slight bodily exertion (walking across not very difficult ground), dyspnea manifested

itself with copious quantities of yellowish-green sputum, the patient came to the hospital.

Status Præsens.—October 29, 1901: The patient was tall, emaciated, with the back somewhat raised; the lips pale blue; syphilitic cicatrices on the forehead; syphilitic ulcer at the roof of the palate. Slight swelling of the supraclavicular glands; carotids slightly atheromatous. Pressure upon the points of exit of the trigeminus (first and second branches) very painful. Thorax narrow, flat, shallow; both supraclavicular and infraclavicular fossæ considerably deepened; inspiratory retraction of the same, of the hypochondrium and epigastrium. Slight inspiratory dilation of the alæ of the nose. Inspiratory and expiratory dyspnea; the expiration occupying a longer time than the inspiration. Right anteriorly above and below the clavicle, slight lessening of sound to the second rib upon percussion, otherwise normal sounds on both sides to the seventh rib, on the left completely concealing the cardiac dulness. Respiratory displacement of the lower borders of the lungs could not be demonstrated. Over the right lung anteriorly above and below the clavicle and in the third and fourth intercostal spaces, absence of respiratory murmur, which is coarse at the base, accompanied with fine, small râles which were plentifully manifest all over, partly dry but for the greater part moist. On the left side also coarse, sometimes hissing breathing; fine râles, considerably more sparse than on the right. In the right axilla also diffuse, fine, moist, besides sparse, dry râles, coarse breathing. Posteriorly on both sides full sound, extending more than a handbreadth beyond the angulus; absence of respiratory displacement, only above the right fossa supraspinata a slight but distinct diminution of sound. Breathing at this point is weakened, otherwise over both lungs posteriorly coarse; dry and fine, to medium moist, râles, most distinct at the base on the right. Sputum rather profuse, frothy mucus, very slightly purulent, permeated by smallest to large air bubbles, slightly movable. Cardiac dulness covered by the pulmonary sound, no apex beat visible, sounds are dull, second aortic sound slightly accentuated. No noticeable anomalies in the abdomen nor in the nervous system, genitalia or urine.

Course of the Disease.—November 4th: Dyspnea and crepitation decidedly diminished, especially on the left; sputum muco-purulent.

November 8th: Catarrh of the left side had disappeared with the exception of some râles at the base posteriorly; at the base on the right still dense, fine to medium, moist and dry râles, also in the lower portions of the right axilla and over the anterior middle lobe. Numerous moist râles were also still noted over the right fossa supraspinata, and isolatedly dry catarrh over the right lung anteriorly above. Dulness was constant at this point. The points of exit of the trigeminus were sensitive to pressure. The sputum was slightly movable, watery-mucus, frothy.

November 13th: The catarrhal phenomena diminished so much that on the left no catarrh at all, and very little on the right over the fossa supraspinata, could be noted, whereas rather dense medium râles could be heard over the base posteriorly, at the axilla and anteriorly, besides coarser breathing.

November 29th: The condition remained unchanged until this date, except that occasionally some dry râles occurred also over the right lung anteriorly and posteriorly. On this day the patient complained of intense coryza, profuse nasal secretion and lachrymation. The points of exit of the trigeminus on both sides remained very sensitive to pressure; moderate injection of the conjunctiva; the marked watery-mucus secretion from the nose unchanged.

December 2d: Dense, moist catarrh also over the left fossa supraspinata, unchanged on the right. The sputum was slightly more purulent than before; the coryza had disappeared.

December 5th: Besides the constant findings on the right, also on the left posteriorly below rather dense, moist, medium to fine, râles; besides, the râles over the left fossa supraspinata persisted until they disappeared on December 10th.

December 13th: The sputum was changeable in quantity until this date; it was never very profuse, moderately muco-purulent. The pains upon pressure over the points of exit of the trigeminus very much lessened.

December 27th: Moist, fine crepitation was noted to be very conspicuous posteriorly right above and at the base, sparse posteriorly below on the left, and marked toward

the axilla and the anterior middle lobe. The patient felt much better and stronger, and the appetite had improved.

January 3, 1902: Dense, moist, mostly medium, râles occurred on the right posteriorly below, and over the left apex posteriorly, sparse, moist râles, which two days later had again disappeared; marked irritation, causing cough; the sputum was unchanged, muco-purulent. There was no longer sensitiveness to pressure at the points of exit of the trigeminus.

January 20th: The patient complained of violent cough and dyspnea. The objective findings remained unchanged; however, on

January 23d: Dense, fine râles were noted over the entire right lung, also slight dry catarrh; the left side was free. The points of exit of the trigeminus again became sensitive to pressure. These bronchitic phenomena disappeared almost entirely until

February 6th, except in the right fossa supraspinata, at the base, toward the axilla on the right and over the middle lobe anteriorly, at which areas quite marked fine and medium râles, similar to the condition about a month previous, could be demonstrated. Subjective well-being. The sputum more fluid, frothy, mucus.

February 9th: The sputum, with unaltered objective findings, was much more purulent than previously.

March 1st: Besides the last-named areas of catarrh noted until then, which had diminished considerably, again quite abundant, medium râles at the left posteriorly below; the points of exit of the trigeminus are much less sensitive to pressure than formerly.

March 8th: The patient complained of profuse nasal secretion, repeated paroxysms of sneezing, with discharge of muco-watery secretion from the nose. The catarrh on the left posteriorly below had disappeared, on the right anteriorly at the axilla and posteriorly it was much less, partly dry, partly moist, râles.

March 15th: On the right posteriorly above continuously sparse fine to medium râles, weakened breathing, diminution of sound. The sputum was mostly profuse, essentially muco-purulent intermixed with air-bubbles.

April 4th: With slight change of intensity of the bronchitic manifestations, they became constantly localized in the right, lower, and middle lobes, also in the right fossa supraspinata. The sputum was profuse ($\frac{1}{2}$ cupful), watery-mucus, slightly purulent, intermixed with air. Naso-pharyngeal findings: Apart from former syphilis, coryza post-influenza. In the larynx signs of chronic catarrh. The general condition was much better, stronger.

The patient was absolutely without fever during the entire course of the disease. The continued examinations of the sputum showed: November 2d, abundant colonies of influenza bacilli and of streptococci. November 15th, likewise abundant colonies of influenza bacilli and of streptococci. December 9th, microscopically numerous influenza bacilli and streptococci. December 29th, numerous streptococci, no influenza colonies. January 23d, isolated colonies of influenza bacilli and of streptococci, principally staphylococcus aureus. February 28th, no colonies of influenza bacilli. March 26th, microscopically numerous influenza bacilli, by culture isolated influenza bacilli, mostly streptococci. April 5th, by culture no influenza bacilli, only staphylococci and streptococci.

In the nasal secretion: January 2d, very large numbers of influenza bacilli, diplococci and streptococci. February 20th, streptococci, a few staphylococci, no influenza bacilli. March 15th, no influenza bacilli.

RESUMÉ: In a patient with emphysema we find, moderate arteriosclerosis, old syphilis, at first diffuse bronchitis which, later, localized over certain areas of the lungs but always fluctuating as to localization and extent, with varying sputum; besides, a rhinitis which varied quite as conspicuously. The course of the disease was entirely without fever. The sputum showed at first very numerous influenza bacilli which subsequently diminished in numbers which, however, could microscopically be demonstrated in large amounts for

over four months; once they could even be shown in the nasal secretion. However, the latter were never found in pure culture, but always associated with other bacteria, mostly streptococci.

This case proves beyond doubt that influenza bacilli are demonstrable in the bronchitic secretion for at least four months, although not continuously but with interruptions.

The question whether the diagnosis of chronic influenza may be established with certainty from this finding cannot be answered in the affirmative at once if we would regard the reciprocity between influenza bacilli and bronchitis as though the latter was caused exclusively by the former; for the influenza bacilli were never found in pure culture, but always in combination with streptococci. However, if we consider the technical difficulties encountered in the culture of influenza bacilli, and if we consider, further, that the influenza bacilli were plentifully distributed over the plate and considerably exceeded the accompanying streptococcus numerically, the conclusion might be fully justified that a chronic bronchitis existed which owed its origin to the co-operation of the influenza bacilli and streptococci, that, in this sense, a chronic influenza rhinitis and bronchitis was unquestionably present. It is not possible here to recognize with certainty the fluctuations between the bronchitis and the amount of influenza bacilli contained in the sputum.

I have the notes of another case which in many respects is very similar to the one reported above but which is particularly characterized in several directions. I shall report the same regarding its general diagnosis and in greater detail with reference to the pulmonary findings.

Patient, J. G., forty-four years of age, factory hand, admitted to the hospital November 20, 1901, still under treatment at the time of this report. Always enjoyed good health formerly; he was attacked by inflammation of the lungs in 1885, from which he entirely recovered. In 1895 he was again confined to his bed with fever, dyspnea, and violent pains in the chest, after having suffered from lead colic one year previously. During the last three years he was periodically subject to dyspnea, marked irritation causing cough, with only slight expectoration of mucus. For three weeks he had again been passing through a period of increased irritation to cough, increasing dyspnea, diminution of appetite and great lassitude; besides, he suffered from gastric disturbances, matutinal vomiting and, finally, frequent desire to urinate (ten to twelve times during the night); he was greatly addicted to drink. Sometimes the patient became subject to actual attacks of suffocation during the night, and that in such a manner that, owing to his dyspnea, he was aroused from his sleep, compelled to sit up and rapidly gasp for breath, and at the same time loud râles could be heard whistling and singing in the chest. The attack lasted from fifteen minutes to an hour and terminated without expectoration. The patient was not able to state whether or not there was a sensation of obstruction in the nose.

Status Præsens.—November 22, 1901: The patient was well nourished, obese; there was conspicuous brown discoloration of the skin of the face and of the genitalia, distinct brown patches upon the mucous membranes of the lips, cheeks and soft palate. Nephritis chronica mixta, pp. interstitialis, subsequent high-graded hypertrophy of the left ventricle of the heart; orthopnea; temperature, 104° F. No sensitiveness to pressure at the points of exit of the trigeminus branches. The thorax had a distinct emphysematous structure. The right supraclavicular fossa slightly relaxed, distinctly in comparison to the left (patient is right-handed), on the right normal percussion to the upper border of the seventh, on the left to the fifth rib, respiratory displacement absent. Inspiration, over the right supraclavicular fossa, still more distinctly over the infraclavicularis up to the second rib; during the first phase it is very sharp, almost

rasping, then for a brief moment of time suddenly interrupted and passing into a less coarse, but still pathologically coarse breathing which is closely related to bronchial respiration; expiration was normally coarse, otherwise the respiratory sounds on both sides anteriorly are at one time hissing, at other times attenuated, accompanied with diffuse, almost throughout singing, catarrh. As anteriorly, right above, so also posteriorly the respiratory sound over the right fossa supraspinata and infraspinata very conspicuously altered, otherwise mostly hissing or coarser or attenuated; besides, all over, especially marked at the bases of both lungs, dense, fine to medium, crepitation accompanied with loud singing, humming and purring. Percussion on both sides normal, one and a half handbreadths below the scapular angle, with absence of respiratory displacement. In the nose rhinitis, in the larynx bronchial catarrh (the anterior portion of the vocal cords slightly atrophied, the posterior portion pachydermically thickened), trachitis. "The turbinated bones pale red, the corpora cavernosa and the lower turbinated bones contracted, the nose was, therefore, so wide on both sides that the posterior pharyngeal wall was plainly visible (in asthmatics a frequent finding during the attack!), rhinitis, laryngitis, tracheitis post-influenzam, asthma nasale (?)" (Dr. Heindl). The sputum was scant, watery-mucus, quivering.

November 29th: The catarrh was much less diffuse over both lungs, mostly dry, only at the base posteriorly moist râles on both sides; the sputum was always uniformly glassy, mucus, viscid, scant.

December 13th: The catarrh is continually diminishing at the base of both lungs, constantly dry, singing, diffuse râles over both lungs. The dyspnea had greatly improved. On February 6th the condition in general was:

Principally dry, singing catarrh, the respiratory sounds at the right anteriorly and posteriorly above unchanged, as if saccated, and continually changing in character in both halves on inspiration. The patient at this date complained of increasing dyspnea, and marked irritation causing cough which even repeatedly led to vomiting; the sputum on this day was more profuse but also mixed with pus; the temperature rose to 100° F., otherwise normal. After four days, on

February 10, 1902: The sputum was again, as before, scant, quivering mucus; the dyspnea had improved. The objective finding was essentially the same as before.

February 15th: The catarrh was materially less than before, principally dry, moist râles at the base on both sides. The condition remained unchanged, with slight variations of the catarrh until

March 4th: When again marked dyspnea occurred, the catarrh became more profuse and the singing râles were audible at a distance; the sputum was mucoid, mixed with pus particles.

March 6th: The sputum, which since the previous day was expectorated considerably more profusely than otherwise, was changed in this respect, partly watery, partly purulently globular, and, in comparison to formerly, much more profuse, consisting almost entirely of nothing but pus corpuscles. The dyspnea was considerable with subjective air-hunger. The objective finding was not noticeably changed.

March 9th: The dyspnea had disappeared, the catarrh at the left posteriorly at the base less than on the right; the sputum was principally mucus and only to a very slight degree purulent.

March 21st: The sputum was scant as before, mucus, quivering, not purulent, intermixed with air-bubbles.

April 1st: With an equal condition of the sputum, the same objective findings with a slight change of the extension of the bronchitic symptoms.

April 11th: Varying bronchitis, sometimes with diffuse, plentiful, dry râles, in particular posteriorly, and at other times decreasing in intensity and extent; however, without entire disappearance of the bronchitis. The saccated respiratory sound which changed in its note during inspiration persisted unaltered at the right anteriorly and posteriorly. The sputum was sparse, mucus, trembling, viscid, quite firmly adherent. The condition was permanently afebrile with a single temporary increase of temperature mentioned above. The strength of the patient increased, and his general condition improved; however, dyspnea persisted even with the slightest movements of the body.

Influenza bacilli were never found in the nasal secretion, in spite of repeated examinations.

Examination of the Sputum.—November 22d, numerous colonies of influenza bacilli (giant growth). December 27th, streptococci and staphylococci, no influenza bacilli, January 2d, especially numerous influenza bacilli, diplococci and streptococci, some few bacilli of Friedländer. January 22d, numerous influenza bacilli, diplococcus, bacilli and streptococci. February 8th, numerous colonies of influenza bacilli, besides bacilli of the group of Friedländer, and streptococci. March 6th, great numbers of influenza and Friedländer colonies. April 18th, numerous influenza colonies. April 30th, moderately numerous influenza colonies, streptococci predominated. May 9th, moderately numerous influenza colonies with isolated colonies of streptococci. May 20th, streptococci, sarcinæ, no influenza bacilli. May 30th, moderately numerous colonies of influenza bacilli, besides streptococci and sarcinæ.

As in the former case, so also in the present one, it was a question of chronic bronchitis in an individual afflicted with emphysema, nephritis and hypertrophy of the heart. Influenza bacilli could almost constantly be demonstrated in the sputum for a period of over six months, once in pure culture, twice almost so. Less even than in the preceding case may we hesitate to speak of a bronchitis chronica gripposa, here also being determined by the view that the influenza bacillus was by no means the sole factor causing the bronchitis but certainly a very important one, in fact, the most important one.

Similar to the clinical picture of this case, in most respects, was the affection of another patient, who at the time of the report was only for a short time under observation. He states the following:

A. Sch., thirty-nine years of age, brazier, admitted to the hospital on February 18th, was discharged cured on April 22, 1902. He was not afflicted with any hereditary disease, and did not pass through any of the diseases of childhood. He suffered from articular rheumatism, fourteen years previously without ill effects. Eight years before admission he became afflicted with malaria; since 1896 he was almost continuously suffering from "catarrhs," and in 1897 he stayed in a hospital for internal diseases for a period of a month, suffering from chronic bronchitis. He was continually subject to recurring catarrhs which at one time improved considerably, at other times became more aggravated, without, however, cough and expectoration having disappeared at any time. When the patient felt worse he was frequently tormented by suddenly occurring "asthmatic attacks" during the night, which manifested themselves in that he suddenly awakened from sleep by shortness of breath, was forced to sit up, to gasp for breath, at the same time becoming subject to violent irritation which produced cough; the attack ceased after a varying duration (from ten minutes to an hour) with moderate expectoration of mucus. For the last three weeks there was a renewed aggravation of the catarrh and increasing dyspnea.

Status præsens and course of the disease which were reported are: The patient was markedly dyspneic, respiration 40, decreasing to 28, to 24 and, finally, to 20 respirations per minute; moderate emphysema of the lungs, diffuse, dry purring and singing catarrh with sharper inspiration, slightly prolonged intensified expiration, besides very isolated moist medium râles. The sputum was profuse, plentiful (a sputa cup full), at first viscid, mucus, slightly purulent, subsequently it became more purulent and, with decreasing catarrh, more watery, mucus, showing very much gray pigmentation, of lesser quantity. The points of exit of the trigeminus were markedly sensitive to pressure. Rhinitis, pharyngitis, laryngitis subacuta post influenzam; no signs of an affection of the accessory cavities of the nose (Dr. Heindl). The sensitiveness to pressure of the points of exit of the trigeminus disappeared, the catarrh gradually became less, until the end of the observation, there remained purring and singing over the posterior portions of the chest; the dyspnea disappeared, the sputum became sparse, mucus, and carrying pigment.

Sputum Examinations.—February 20th, numerous influenza colonies, sparse staphylococci. March 15th, numerous influenza colonies with occasionally colonies of streptococci and sarcinæ. March 15th, very numerous influenza colonies with sparse staphylococci. April 20th, numerous colonies of influenza bacilli and streptococci.

The condition of the patient was constantly afebrile.

The two first-named cases proved, as already mentioned, that an influenza bronchitis may exist for months, and that a chronic influenza bronchitis within the meaning characterized by us unquestionably occurs. The third case is the more interesting in this respect for as long as examinations of the sputum were made—which was the case for a period of eight weeks—influenza bacilli were found in the sputum almost constantly, at least for a period of four weeks. These cases, therefore, demonstrate the correctness of referring to such cases as chronic afebrile influenza bronchitis.

As far as I am able to determine from the literature, only one author has called attention to this fact from a clinical aspect, namely Finkler. This affection has been so little determined in a clinical sense that Leichtenstern¹ in his otherwise excellent exhaustive monograph on influenza does not refer to it at all, although Finkler's very thorough work had been published a year previously. I am able by reason of my own observations to confirm word for word what Finkler² has written regarding chronic influenza bronchitis. Only my observations—and this in my opinion is a very important point—appear to me to be of especial value, in so far as Finkler only refers to chronic bronchitis which in connection with an acute influenza had almost become permanent. In my cases a proof of this sort was absolutely impossible. It is true the first of my patients stated that in 1889 he had suffered from influenza but of such a mild grade that it did not interfere with his occupation and for three or four years afterwards he remained entirely well. Both of the other cases, in spite of careful, repeated questioning, were not able to remember any acute febrile affection that bore the slightest resemblance to influenza, either during the pandemic of 1889–90, or in succeeding epidemics. These two patients, and probably also the third one, accordingly appear to have contracted influenza without the affection having produced demonstrable symptoms, perhaps in the form of a simple "cold" which did not prevent them from attending to their usual occupations; the influenza, so to speak, having appeared in an *insidious* manner. From a diagnostic point of view, I desire to lay particular stress upon this point. Who would at once have thought of influenza in the above three patients? I believe I may answer with Finkler: "No one would have suspected that a chronic influenza was present in these cases." I believe that this view is founded most effectually on the fact that two of the patients repeatedly were in other hospitals, one in a medical clinic and, as I was able to learn from a perusal of the respective case history, on no occasion and at no time was the possibility of influenza thought of. I do not hesitate to admit that the second case was twice a patient in my wards and I also failed to establish a correct diagnosis regarding the cause of the bronchitis which in both instances was of exactly the

¹ *Leichtenstern*, Influenza in Nothnagel's Specielle Pathologie und Therapie. Wien, Hölder, 1896.

² *Finkler*, loc. cit.

same character as during the last period of observation, and probably chiefly for the reason that a single examination of the sputum was ordered then in which I expressly advised looking for influenza bacilli, and their absence caused the unjustified conclusion that a chronic influenza was not present.

If we concern ourselves more closely with the clinical side of these cases of chronic influenza bronchitis, we must admit that it does not present distinct clinical criteria which are at all peculiar to it. At one time a dry, at another time a moist, catarrh, the location of which varies; at one time diffuse, at another time localized to distinct areas of the lung in the same patient, and with this not infrequently even being limited to the upper lobe. It appears to me that the constant finding, in our second patient, of the peculiarly saccated varying respiration (I might almost say metamorphosing) over the right upper lobe, is well worth emphasizing. I believe that I am not mistaken in connecting this finding with the difference of calibre in the course of the bronchus possibly with a spindle shape of the bronchus which again is in complete harmony with the causation of bronchitis due to influenza bacilli. I desire to lay particular stress upon a special characteristic of the bronchitis and upon the dyspnea connected with the same. I refer to the *singing, sighing* character of the dry catarrh. Who would not be reminded of a chronic asthmatic bronchitis in view of the afebrile course of the disease, the presence of emphysema, a condition common to all three patients, particularly in view of the above-described nocturnal asthmatic attacks (occurring in the two last-mentioned patients), of the accompanying paroxysms of sneezing, of the viscid quivering condition of the sputum, of the peculiarity of the catarrh? A confusion of the two affections is much more apt to occur as the condition of the nose in the second case presented a remarkable analogy with the findings in true nervous bronchial asthma. However, an actual confusion of these conditions will be avoided if we call to mind the postulate which was first created by the observation, that a chronic influenza bronchitis may clinically almost completely resemble chronic asthmatic bronchitis and that the possibility of the presence of the former must also be considered when the latter is likely to be present. After our differentio-diagnostic consideration has progressed thus far the definite diagnosis becomes easy. The painfulness of the points of origin of the trigeminus nerve (respectively of the accessory cavities of the nose and pharynx) may be utilized in favor of the diagnosis of influenza and as opposed to that of bronchial asthma. Above all, however, it depends upon the examination of the sputum. In the latter case (bronchial asthma), Charcot's crystals, Curschmann's spirals, eosinophile cells, marked absence of bacteria; in the other instance (influenza) bacilli eventually with other micro-organisms in great numbers and—according to my investigation—besides mucus and some epithelium, also varying quantities of polynuclear leukocytes.

It seems to me that two other factors which result from an exact consideration of the above-named cases are worthy of especial mention. I wish to call attention to the fact that it was possible in all three cases to determine besides the chronic influenza bronchitis, emphysema of the lungs. I have notes of three other cases which occurred during the winter of 1902, in the first and second of which the influenza set in acutely, whereas in the third

case the attack was less noticeable and more insidious showing the catarrhal respiratory type and subjectively also the signs of increased dyspnea and irritation to cough, and with profuse expectoration. These three patients, at the time of the report, were still under treatment in the hospital. The first of the patients, M. D., thirty-eight years of age, blacksmith helper, who allegedly one year previously, had passed through an inflammation of the lungs, was said to cough frequently since then and, six weeks before admission to the hospital, had become sick with chills, stitches in both sides, coryza and great prostration. He reported that subsequently he recovered, again to become affected four days previous to his admission to the hospital, with chills, coryza, pains in the throat, marked cough, and decided inclination to prostration. With a temperature that once reached 99.9° F., but which was otherwise entirely normal, he presented besides, emphysema, a generally dry bronchitis, moist only at both sides of the base, with always profuse, watery-mucus, rarely purulent sputum. The points of exit of the trigeminus at the nose were extremely painful, probably the signs of an affection of the accessory passages, rhinitis, pharyngitis, and acute laryngitis. The sputum was examined from March 8th to May 30th, and numerous colonies of influenza bacilli, besides colonies of diplococci and streptococci and plentiful colonies of the group Friedländer and streptococci, were always found to be present. Therefore, the acutely appearing influenza had passed into the chronic form, which even at the time of the report, i. e., eighty-four days after it had been positively determined, could be demonstrated clinically and bacteriologically. Similar conditions prevailed in the case of the second patient who, however, acquired an intercurrent influenza pneumonia of a lobular character which, up to the time of the report, had not terminated in resolution. J. P., seventy-five years of age, street-cleaner, who had suffered from shortness of breath for the past three years was said to have become affected two months previous to admission to the hospital, after a drenching, with chills, lassitude, coryza, and cough, accompanied with stitches in the side. The patient, who at first was afebrile, showed diffuse, purring, and singing catarrh, besides emphysema. The catarrh diminished during the first days in the hospital; there was intercurrent pleural friction on the left; the sputum was always sparse and mucus, showing bacteriologically numerous colonies of influenza bacilli besides colonies of the group Friedländer. Suddenly, without chill, a rise of temperature up to 101.7° F. (rectal temperature) took place with a development of lobular infiltration in the right axilla, the sputum from then on being almost exclusively purulent, and again contained numerous influenza bacilli besides streptococci and staphylococci. The pneumonia still persisted at the time of the report (sometimes bronchial breathing and crepitations could be heard over the focus with only slight diminution of the percussory sound, at other times only indistinct breathing, crepitation, or fine, mostly ringing, râles and always increased vocal fremitus besides, until a few days previous to the report, pleural friction on the right). The sputum was muco-purulent, containing at the last examination on May 30th, numerous colonies of influenza bacilli with streptococci; during the previous examinations, on March 27th and April 30th, besides numerous colonies of influenza bacilli isolated catarrhal micrococci and numerous staphylococci.

Finally, the third patient, J. K., fifty-four years of age, who suffered from shortness of breath and cough for four years, noticed, five months previous to his admission to the hospital, an aggravation of the affection. The objective examination showed almost complete absence of fever, emphysema and diffuse, dry catarrh that was moist at the base. The catarrh diminished during his stay at the hospital, however, at the time of the report, moist fine râles, besides diffuse, sparse dry catarrh could still be demonstrated at the base of both lungs; the subjective disorders became less, the same as in the other two patients, with mostly rather scant mucus and also slightly purulent sputum. The latter was examined bacteriologically five times and always showed numerous colonies of influenza bacilli besides streptococci and staphylococci, and that during a period of seven weeks.

All the above-described cases of bronchial influenza, six in number, are such, therefore, as were simultaneously combined with emphysema of the lungs. But what we know now regarding the relations of influenza and pulmonary influenza, that an acute influenza intervenes in emphysematous patients frequently causing even lethal termination: We were apprised of this fact by the pandemic of 1889-90, although it was quite generally known even before the latter (Biermer).¹

However, our cases are also of interest in another direction which has not yet been sufficiently determined clinically, according to my opinion. They prove that in emphysematous patients an aggravation of the disease of which they complain, especially of the cough and the shortness of breath, may be based upon an intercurrent influenza which may either occur acutely or insidiously in a less noticeable—I might say—chronic manner; it may then become firmly established and in both instances persist for weeks and for months (according to my own observation of over six months which period, however, may surely be surpassed). At the same time the influenza affection does not cause any other phenomena than that of the simple bronchitis. All other half-way characteristic influenza symptoms are absent. I only wish to once more point out in particular the painfulness on pressure of the points of exit of the trigeminus, respectively of the accessory cavities of the nose in many cases. It is true, they are not pathognomonic of influenza, although, in my opinion, they are suggestive of an influenza infection, for I have found it to be very prominent also in streptococcus infection of the respiratory tract and recently also in a case of erysipelas.

These cases prove the correctness of what Finkler² stated seven years ago which, strange to say, however, as it appears to me, has not been generally noted. He said: "Influenza occurs frequently with chronic bronchitis of a different etiology. We very frequently observe patients who have coughed for a long period of time, in whom an old catarrh was present, with apparently passive bacteria, in whom the influenza affection is added. This is usually considered to be an aggravation of the prevailing bronchitic condition."

However, my observation suggests another thought, namely that emphysematous patients may become injured by influenza in an entirely different man-

¹ Biermer, *Influenza in Virchow's Handbuch der spec. Pathologie und Therapie*, Stuttgart, Enke.

² Finkler, *loc. cit.*

ner than has been known until now. Not in that an acute influenza infection with its severe bronchitis and pneumonia and the presence of an existing emphysema represents an extremely severe complication: not in that, owing to processes of induration and bronchiectasis, the emphysematous are doubly endangered but the emphysema may become generally aggravated in that a chronic bronchitis establishes itself with the consequences of the increased cough and of the increased dyspnea which may exacerbate and asthmatic attacks occur. I even desire to express the thought that the existence of numerous cases of emphysema may be directly due to such an influenza bronchitis. For who knows how many of the aggravations of their affections, through which my patients have formerly passed, may not be the same as those observed by me, and ascribed to an intercurrent influenza affection? However, this is only a supposition of my own, which might find support in the conception of the French, according to which influenza is able to produce a permanent weakened condition of the bronchial musculature, a bronchoplegia. I am not able, however, to furnish any positive proofs either for the latter or for my own opinion as stated above.

A second factor which may be derived from the observation of our cases concerns the bacteriology of chronic bronchitis. I have noted, the same as Finkler,¹ that in by far the greatest majority of examinations not only the influenza bacilli could be demonstrated in the sputum but they predominate, besides other bacteria such as streptococci, diplococci, bacilli of the group Friedländer, micrococcus catarrhalis and staphylococci. In continuous examinations of the sputum, it might happen that at times influenza bacilli would not be found in the sputum, whereas either before or afterwards, large numbers of them would be determined, this being a distinct demonstration that a single examination of the sputum is, under no circumstances, sufficient. The fewer the influenza bacilli the more abundant became the other bacteria, especially streptococci and pneumococci until the latter predominated and the former disappeared entirely. However, it is very difficult to state whether the influenza bacilli then actually disappeared completely from the diseased organs—quite apart from the difficulty and shortcomings of the method of examination and of the minimal quantity of the material examined. I consider the contrary to be much more probable and believe that the influenza bacilli, even though they are entirely absent from the sputum, may still remain for a longer period of time, in the diseased human organism in a latent condition, so to speak. In my opinion, this is indicated from a clinical aspect, by the permanence of certain phenomena (continuance of catarrhal manifestations in certain areas of the lungs), but especially by the entirely unnoticed, insidious recurrence of the influenza affection which, after all, can be much better explained by a recrudescence of the chronic insidious process than by a reinfection from external sources, and by the absence of all half-way typical symptoms of influenza. It is well known that our bacteriological knowledge is in accord with this assumption; for we know that the influenza bacilli, especially in the tuberculous, may persist in the human organism for six months (Pfeiffer²) and even almost a year and a half (Finkler³) after recovery from grippe.

¹ Finkler, *loc. cit.*² Pfeiffer, *loc. cit.*³ Finkler, *loc. cit.*

However, as to the simultaneous occurrence of influenza bacilli and the above-named bacteria, it confirms the fact which is also extremely noticeable in acute influenza, as is well remembered. It is a further confirmation of a statement of Finkler, that he (Finkler) "has never seen a chronic bronchitic affection which had remained permanently, which was due alone to a single variety of bacteria; but one variety of bacteria may retain prominence, it may be the stabile kind, to which alternately sometimes one, sometimes another, form of bacteria may be added."

The finding of influenza bacilli may be of the greatest value for the clinico-etiological conception of an afebrile bronchitis, as I believe is sufficiently confirmed by my exhaustive explanations. However, the finding of influenza bacilli is of another, by no means less important, significance, the recognition of a fatal affection in individuals whose respiratory and circulatory apparatus had been previously injured. I do not mean to refer again to those cases with which we are familiar from the periods of the influenza epidemics and pandemics, in which a clinically most probable influenza infection caused the death of the affected person in the presence of a freely existing pulmonary emphysema or of a preexisting disease of the circulatory system, whereas these affections in themselves would have been compatible with the continuance of life. Already Biermer,¹ Drasche² according to observations of the pandemic of 1889-90, and also many after them, have furnished numerous material by reason of clinical investigations as did also Richter³ and Paltauf,⁴ by reason of anatomical investigations from the recent last great epidemic of 1891-92. It is my intention to call particular attention again to the fact which has been anatomically known for quite a while, which is clinically scarcely appreciated, that an apparent simple bronchitis which clinically was not characterized by any character whatever may be based upon an influenza infection and that a serious, often lethal prognosis, at the moment of its recognition is justified in those cases in which preexisting affections of the lung and of the heart would not justify such a prognosis.

I have observed two cases during the winter of 1902-03, quite similar to the previously-described cases, they were patients, one forty-five, the other fifty-two years of age, each of whom stated that they had suffered for years from catarrhs which decidedly depended upon the weather, which generally became worse during the autumn and winter, and which improved again during the summer months. Such a slow aggravation of the catarrh, that is of the shortness of breath, of the cough and of the sputum, which took place entirely without fever, according to the perception of the patient, caused them to apply to my clinic. The objective finding in both patients showed moderate emphysema of the lungs, diffuse, mostly dry catarrh, moist at the base of both lungs, with fine râles, medium strong dyspnea, symptoms of a weakened action of the heart, in one instance with edema of the lower extremities, the other without marked manifestations of stasis, and both with muco-purulent sputum and intermittent rise of temperature to 99.5° F. The clinical diagnosis in both instances was myodegeneratio cordis, emphysema pulmonis utriusque, bronchitis diffusa; the bacteriological examination of the

¹ Biermer, *loc. cit.*

² Drasche, *loc. cit.*

³ Richter, *loc. cit.*

⁴ Paltauf, *loc. cit.*

sputum in both instances showed numerous colonies of influenza bacilli, in one instance staphylococci, in another streptococci and diplococci. In both cases, four days after admission to the hospital, the fatal termination occurred, and in both instances the pathologists who were fully able to confirm the clinical diagnosis by the autopsy became convinced that the influenza infection, which had also been demonstrated anatomically, with its localization, above all, in the smaller bronchi, had caused the premature death of both patients ("the bronchial mucous membrane, especially of the smaller bronchi, was markedly congested and swollen, covered with yellow pus, the retro-bronchial lymph glands, in size larger than a hazel-nut, showed medullary infiltration. The mucous membrane of the trachea and of the larynx was only moderately congested").

Such cases must always convey to the clinician the grave admonition, even in apparently simple bronchitis of which the patients complain only as exacerbations of the catarrh already existing in the lung which is not accompanied with much rise of temperature and which clinically does not manifest any stigmata of influenza whatever, to think of influenza, even in such cases in which there can be no question of the presence of an epidemic of influenza. If the bacteriological examination, which must be made at once, reveals the presence of influenza bacilli it involves a serious prognosis if symptoms are present of preexisting cardiac asthenia even if the latter is not of a high grade. For as epidemic, so also does sporadic influenza which apparently occurs as an insignificant bronchitis, affect, above all, the myocardium, and exhaust its remaining strength.

Sporadic influenza may be combined in the human organism with *tuberculosis of the lungs*, the same as it may supervene upon preexisting affections of the heart, upon bronchitides and upon emphysema of the lungs, at one time occurring in the form of an acute infectious disease, at other times being concealed under the guise of a chronic bronchitis. Regarding the frequency of the combination, it does not behave any differently from epidemic grippe. It is well known of the latter, that when it becomes established in tuberculous patients, it represents an extremely dangerous, lethal combination. The same holds true also of sporadic influenza if conclusions are drawn, above all, from the results of pathologico-anatomical investigations. The most exhaustive examinations, in my opinion, were made by Kretz.¹

It is difficult to form a precise judgment from a clinical standpoint, for I believe that the majority of clinicians, who all emphasize the great danger of influenza to the tuberculous, base their judgments upon observations of the period of the epidemics. Only Finkler,² so far as I can see, constitutes the sole exception and even he becomes convinced that the dangers of acute and chronic influenza to the phthisical patient are enormous.

I also found, during the winter of 1902-03, among the great number of patients with pulmonary tuberculosis and with an exact bacteriological examination of every one of them, 12 tuberculous patients in whose sputum influenza bacilli could be demonstrated besides tubercle bacilli. Of these 12 patients 5 had succumbed; however, the tubercular changes alone (partly only in the lungs, partly in other points as well) had advanced so far in all of these

¹ Kretz, *loc. cit.*

² Finkler, *loc. cit.*

patients that their deaths were sufficiently warranted by these conditions. However, I must mention and must particularly emphasize the fact that especially in one patient, in whom an extraordinarily marked retraction in the region of the left upper lobe with the most undoubted symptoms of infiltration and cavity formation became prominent clinically, and in whom these changes were ascribed as due to the tubercle bacillus, in this entire region calcareous induration with bronchiectasis was found at the autopsy without any tuberculosis whatever; an induration which, according to the statement of the pathologist, Prof. Kretz, was to be ascribed solely to chronic influenza but certainly not to the tubercle bacillus. This was another case which again proves that in apparently tubercular phthisis of the lungs extensive areas of the lungs may be physically changed, it is true, as has been correctly assumed clinically, not, however, owing to the activity of the tubercle bacillus, but instead to the influenza bacillus, which, as is well known, is conspicuously capable of producing indurative processes.

The intercurrent influenza in the other tuberculous patients ran its course under the almost typical picture of acute influenza which was only slightly protracted and in which, besides slight bronchitic and rhinitic symptoms (also phenomena on the part of the accessory cavities), the general manifestations became prominent, above all, and the symptoms of influenza receded entirely; or an acute febrile aggravation of the affection became manifest with distinctly demonstrable extension of the process of infiltration, which was probably due to the influenza infection, in which very soon resolution of the acute infiltration took place or did not occur completely, but in which the influenza bacilli disappeared again from the sputum in a very short time; or, again numerous influenza bacilli were found for weeks in the sputum of the moderately febrile patients and no alteration in the clinical picture which permitted the determination of cavities and of infiltration around them, could be demonstrated. Therefore, I was not able to state with certainty from whence the influenza bacilli originated and which rôle they played in the above cases. Finally, it was a question of two and, perhaps, of three observations which, in my opinion, are of such a prominent clinical interest that I believe I am justified in reporting them more in detail.

In the first case it was a question of an influenza infection in a tuberculous individual in whom, first influenza undoubtedly aggravated the tuberculous process; and second, in whom a very peculiar manner of occurrence could be determined which, up to the present, as far as I could see, was not noted anywhere and which, similar to Finkler¹ I desire to designate as the **intermittent form of influenza**.

H. R., twenty-three years of age, admitted October 15, 1901, discharged February 1, 1902. Patient was hoarse for six years, allegedly subsequent to violent cough. Since the summer of 1900 he suffered, upon marked bodily exertion, from shortness of breath and palpitation of the heart. Since the spring of 1901 he had noted general lassitude, debility; he became easily tired, had night sweats, stitches in the side, sensation of pressure upon the chest, violent cough with expectoration, but never hemoptysis. Since October, 1901, fever, loss of appetite; not until August did improvement take place

¹ Finkler, *loc. cit.*

again; however, with persisting moderate cough. After October 8th, he again complained of stitches in the side, marked cough, shortness of breath, and frequent coryza.

Status Præsens.—October 16th: Temperature normal, pulse 86, respiration 88. Normal percussion over the lungs on the right to the sixth, on the left to the fourth ribs, posteriorly to the eleventh spinous process; distinct respiratory displacement all over. Abundant, diffuse, either dry or moist, small to medium râles. The respiratory sounds slightly forcible. In the larynx the vocal cords were slightly congested and thickened as was the interarytenoid mucous membrane; night sweats, otherwise normal conditions.

October 20th, patient coughs less; râles have become more sparse. October 25th, râles had almost disappeared, subjective well-being.

October 26th to November 4th: Continued, unchanged well-being; only very isolated catarrh over the lungs. No sputum.

November 5th to 6th: A sudden rise of temperature occurs without chill up to 101.9° F., which on November 6th declined to 99.3° F., subsequently becoming normal again; distinct catarrh over the apices of the lung anteriorly and posteriorly; coarse breathing especially over the left clavicular fossæ; the spleen which until then could not be felt became palpable, about half a finger breadth below the costal arch.

November 7th to 17th: With subjective well-being the phenomena over the left apex remained, with normal temperature, and respiration 24. The scant mucus sputum of November 27th did not contain any influenza bacilli but mostly streptococci.

November 18th to 23d: The temperature rose without chill from 97.9° F. at 6 A.M. to 102.9° F. at 6 P.M. which, within the next five days persists up to 103.5° F. with sweats occurring every night, great acceleration of respiration to 36, and increase of the pulse frequency to 120 per minute. The borders of the lungs are distinctly displaced by about one intercostal space; on the right diffuse, partly dry, partly moist, small to medium râles and dry râles over both lungs. The respiratory sounds over the left apex both anteriorly and posteriorly are distinctly protracted. The sputum is profuse, slightly streaked with blood which does not contain tubercle bacilli; however, on November 19th, numerous colonies of influenza bacilli in pure culture with marked nightly perspiration; recession of the bronchitic manifestations to traces occurred in the course of five days, patient feels well.

November 24th to 28th: Over the left apex anteriorly and posteriorly dulness which gradually became more distinct, with coarser, prolonged expiration and râles. Since then diffuse, mostly dry catarrh with *volumen pulmonum auctum*, quite profuse watery mucous sputum, perceptibly mixed dyspnea appeared, increasing anemia, night sweats.

November 29th to 30th: The catarrh receded rapidly, only isolated dry râles posteriorly with the exception of the left apex which constantly presents, anteriorly and posteriorly, dulness, coarser protracted expiration, non-metallic moist and dry râles. The temperature had been normal since November 23d, no more night sweats, the respiration was much freer and easier and had diminished from 26 to 24 per minute. *Volumen pulmonum auctum* still persisted.

December 1st to 2d: Stitches in the side and pleural friction upon the left in the vicinity of the seventh rib. Renewed rise of temperature, intermittent in type to 102.6° F. which continued to December 7th, falling gradually. Simultaneously again dyspnea, compact, moist, middle to small-sized râles, otherwise lessened dry catarrh, diffuse over both lungs. Pronounced irritative cough. Expectoration quite profuse, muco-purulent, quite plentiful tubercle bacilli found for the first time. Besides plentiful influenza bacilli again, with these streptococci and the staphylococcus aureus and the micrococcus catarrhalis.

In the larynx a distinct tubercular ulcer upon the left vocal cord. Since December 3d, complains of marked headache. Temperature normal up to December 24th, the maximum being 100° F., night sweats returned. Gradually developing dulness also at the right apex with rough almost bronchial expiration and limited catarrh. Otherwise the catarrh of the left axilla and pleural friction, dyspnea and marked cough have disappeared; in the sputum from December 16th to 24th, no influenza bacilli but only streptococci and staphylococci.

December 25th to 27th: Another rise of temperature to 103.3° F. on the first day, with a gradual decline. Again marked cough, increasing dyspnea and hoarseness, the same changes at the apices, diffuse sonorous and sibilant râles and upon the left pos-

teriorly also moist medium râles. Respiration 28, pulmonary borders dilated, although movable. Sputum scant, mostly mucoid but slightly purulent. Influenza bacilli colonies besides streptococcus and staphylococcus albus are again present in the sputum.

December 28, 1901, to January 5, 1902: The diffuse catarrhal process may still be demonstrated, the changes in the apices increase rapidly as the extent of the dulness over the apex posteriorly reaches to a finger breadth below the spine of the scapula, upon the right distinct bronchial inspiration and expiration with large-sized râles.

January 6th to 20th: The diffuse catarrh diminishes so that now only local, dry and moist râles may be heard on the left posteriorly and in the axilla. The acute pulmonary dilatation retards, the apex changes remain unaltered. The condition in the larynx is markedly improved, swelling and redness of the vocal cords have markedly declined, the ulcer has healed. The temperature, with the exception of a single rise to 100.4° F., has been continuously normal, with subjective well-being without night sweats. The objective findings and the condition improved until the patient was discharged from the hospital on February 1st.¹ The sputum examined, however, on January 24th, still contains numerous colonies of streptococci and staphylococci.

The history described above is especially instructive in two directions. It primarily illustrates how a tuberculosis of the lungs, which at the onset was surely of a very limited extent and which could scarcely be noted clinically without the microscopical demonstration of tubercle bacilli in the sputum, progressed to a marked degree under an attack of influenza and led to a marked infiltration of both upper lobes, with the expectoration of quite large amounts of tubercle bacilli.

It furthermore represents a form of acute influenza with quite an abnormal course clinically, which I desire, as stated previously, to designate as an *intermittent form of influenza*; it is characterized in that the patient in repeated febrile attacks, lasting but a few days, and separated from each other by afebrile intervals of various lengths, becomes attacked by an acute influenza bronchitis which at one time is localized, at another time diffused, and which during the afebrile period almost entirely or actually recedes.

Finkler,² also refers to intermittent influenza and understands by it that form of grippe which in the course of a chronic grippe infection of the bronchi permits the disappearance and at other times the reappearance of influenza bacilli in the sputum, with a coincidence of an acute aggravation of the affection during the period in which the influenza bacilli become very numerous in the sputum. It is difficult to state whether this condition was also present in my case, for to do this more frequent examinations of the sputum, also during the afebrile period of the disease, would have been necessary. Nevertheless, the fact that the patient shortly before being discharged from the hospital, with relative subjective well-being, complete absence of fever (in spite of bilateral tuberculosis!), still harbored numerous influenza bacilli in the sputum, does not render this consideration very probable. My observation rather proves that influenza bacilli are capable of producing from time to time in the human organism, especially in the bronchi, acute pathological manifestations which recede after a brief period, to recur again after a short time and to disappear and to reappear at another time. We are led

¹ A few days prior to this report the patient was again admitted to the clinic; the bilateral apical tuberculosis had increased in extent and a daily hectic fever was present. The sputum again showed numerous influenza colonies.

² Finkler, *loc. cit.*

involuntarily to explain this fact in such a manner that the patient, owing to the manifest infection with influenza bacilli, becomes immune, loses his immunity after a brief period of time and furnishes a new soil for renewed manifestation of the disease, brought about under the influence of bacilli which most probably have remained latent in the organism. In this sense, more clinical than bacteriological, I consider the expression "intermittent form of influenza" to be fully justified.¹

If the aggravating influence of an influenza affection appears strikingly enough in the above-described case, this is still more evident in the following instance which directly proves that a latent tuberculosis of the lungs becomes manifest by an intercurrent influenza affection, giving rise to rapid progression and owing to the co-operation of both infections, soon leads to the death of the patient.

E. F., aged nineteen, clerk, admitted to hospital on February 11, died March 8, 1902. Both parents suffered from pulmonary disease, brothers and sisters healthy, the patient has always been well. Sixteen days ago onset of the affection with sudden fever, marked headache, coryza, pains in the root of the nose, lassitude, pain in the limbs, and a single attack of vomiting. For twelve days she suffered from attacks of dyspnea and night sweats.

Status Præsens.—The patient was of quite robust appearance, well-nourished; she complained of headache; marked painfulness upon pressure at the points of exit of the first and second branches of the trigeminus. Marked lachrymation; nose was obstructed, the lips livid, eruptions of herpes appeared in the left corner of the mouth, the tongue was coated, moist, trembling. The left upper thorax distinctly relaxed during respiration. Both supraclavicular fossæ dull, on the left also the clavicle, otherwise normal percussion, on the right to the sixth, on the left to the fourth, rib. Right anteriorly over the supraclavicular fossa extremely dense, medium to fine râles, non-metallic, were very close to the ear, besides also dry râles fully covering the respiratory sounds. Over the left supraclavicular fossa an indistinct respiratory sound was heard, numerous dry coarse râles which, with coarser breathing are diffusely audible over both lungs. Posteriorly to the right over the spine of the scapula, and below the latter to the angle of the scapula, distinct lessening of the note as well as on the left superiorly to one finger breadth below the spine, otherwise normal percussion to a finger breadth below the angle of the scapula; respiratory displacement was present. To the right in the supraspinatus and infraspinatus fossæ tubular bronchial breathing, dense medium and fine non-metallic râles, besides some dry râles; otherwise harsh breathing with dry and moist râles. Over the left supraspinatus fossa very close indistinct inspiration and expiration, dense medium to small sized râles, non-metallic in character with dry râles which became less distinct lower down. With this, coarse vesicular breathing. At the

¹ I should like to add that in my opinion an analogous intermittent form of influenza may exist for months or for years as a substantive affection. Thus I recently saw a patient who for about three years, every two weeks during the inclement season, later on every three or four weeks, but not at all during the summer, became affected by an acute rhino-tracheo-bronchitis accompanied with fever and with dyspeptic disturbances and quite insignificant constitutional symptoms; the cause of the affection was not quite clear. I examined the sputum and found extraordinarily large colonies of influenza bacilli. This finding renders it quite likely to me—owing to its isolated occurrence it naturally does not prove anything—that the patient suffered from an intermittent chronic influenza. *Filatoff (loc. cit.)* has also described similar cases (repeated attacks of fever with and without bronchitis but mostly with coryza and again with afebrile disturbances of health occurring at regular intervals), which he explains as chronic influenza. Unfortunately there was no bacteriological examination, the decisive test is therefore missing.

left base, close to the spinal column, an area of consolidation about the size of an apple with dense small râles, diminished respiration, scarcely increased vocal fremitus. The left axillary region shows intense diffuse catarrh. In the infraspinal and supraspinatus fossæ upon the right distinctly increased vocal fremitus and vocal resonance. No sputum. Temperature varied between 100.8° F. and 104.4° F., pulse 112, respiration 28. Besides a functional murmur over the pulmonary area, normal cardiac conditions. Arteries soft, tension below normal. Number of pulse beats when sitting 12 more than in the recumbent posture. Slight meteorism. Spleen one-half finger breadth below the margin of the ribs, soft, otherwise nothing pathological in the abdomen. In the urine trace of serum-albumin, no diazo-reaction. In the blood very sparing fibrin net, no leukocytosis. Marked painfulness of the muscles of the lower extremities.

Course of the Disease.—February 13th: The general impression of a severe intoxication; very pronounced dyspnea. With the same pulmonary findings upon this date, distinct metallic, medium sized râles over the right supraspinal fossa. Upon the right over the supra- and infraclavicular fossæ bronchial inspiration and expiration. Otherwise pulmonary findings unchanged. Sputum quite profuse, predominantly purulent. Tubercle bacilli are present but few in number. Night sweats; remittent fever reaching 100.3° F.; respiration 32.

February 14th to 17th: With continued remittent fever up to 104° F., increasing respiratory frequency 37 to 40 there is also heard upon the left, posteriorly above, bronchial respiration and metallic râles. Over the left base in the area of dulness today metallic small râles. Vocal resonance distinctly increased.

February 18th to 23d: Remittent fever, reaching 104.4° F. persisting, continued dyspnea; sweating; cyanosis increasing, advancing emaciation, dulness posteriorly above, upon the left, increasing in intensity and extent almost reaching to the middle of the scapula; distinct bronchial breathing. Over the dulness at the left base conspicuous dense small râles. In the urine with traces of albumin a constantly negative diazo-reaction, urobilin in large amounts. Anteriorly upon the right an increase of the dull area reaching to the fourth rib, bronchial inspiration and expiration, crepitant râles. Anteriorly upon the left up to the upper border of the second rib an empty, then marked tympanitic note up to the point of cardiac dulness. Decided cyanosis of the lips and cheeks.

February 24th to 28th: Without a change in the condition of the lungs there is noted posteriorly upon the left over the dull area distinct inspiration and expiration with marked catarrh. Posteriorly, bilaterally above, metallic medium to large-sized râles. Posteriorly, below, upon the right, distinct pleural friction. Anteriorly, upon the right completely hollow note up to the second rib then dulness up to the fourth rib. Over the supra- and infraclavicular fossæ bronchial inspiration and expiration, profuse metallic small and medium sized râles. Sputum quite sparse, predominantly purulent. Upon repeated examination but very few tubercle bacilli can be found. Number of leukocytes = 5,000.

First to the 4th of March, unchanged conditions regarding lungs and pleura. Remittent temperature reaching 105.3° F., pulse reaching 140, respirations 44; marked cyanosis. The patient presents the picture of a severe intoxication. At night delirium, sweats, very marked cyanosis of the cheeks and lips. Diazo-reaction constantly negative.

March 5th to 8th: Infiltration phenomena anteriorly and posteriorly upon the right, increasing in extent; fresh eruption of herpes in the middle of the upper lip, edema of the lower extremities. The mind becomes more and more clouded, sputum quite spare, purulent, but few tubercle bacilli. Remittent temperature reaching 104° F. Exitus letalis.

Bacteriological Examination of the Sputum.—February 12th, streptococci colonies and colonies of the micrococcus catarrhalis (besides another bacillus being especially studied in the Institute of Prof. Kretz at that time); no influenza bacilli colonies. The same findings upon February 15th. February 23d, particularly profuse influenza bacilli colonies and streptococci colonies. February 27th, profuse influenza bacilli colonies and colonies of the staphylococcus aureus. Individual streptococci colonies. March 4th, particularly profuse influenza bacilli colonies side by side with streptococci and staphylococci.

Bacteriological Examination of the Nasal Secretion.—Upon February 12, 1902, pro-

fuse influenza bacilli colonies besides colonies of the previously mentioned still unknown bacillus.

Bacteriological Examination of the Blood (Venous Puncture).—Sterile upon February 14th. Our clinical diagnosis was: Infiltratio pulmonis utriusque lob. sup., pp. dextri partim e tuberculosi, partim ex influenza; Rhino-Laryngo-Tracheo-Bronchitis acuta per bacillos influenzæ; Pneumonia lobular. pulmon. sin. lob. inf.; Pleuritis fibrinosa dextra; tumor lienis acutus, tuberculosis miliaris terminal. (?)

The exact clinical conception which we formed of this case was this, that the pathological changes, especially the infiltration of both upper lobes, was due to a combined action of the influenza and tubercle bacilli (assisted by the streptococci). The acute bilateral infiltration therefore was brought about by a mixed infection.

Autopsy diagnosis (Prof. Dr. Kretz): Phthisis tuberculosa loborum superiorum pulmonum pp. dextr. Tbc. granular. pulmonum et miliaris pleuræ dextræ. Peribronchitis tuberculosa et pneumonia lobular. confluens. Pleuritis fibrinosa dextra; tracheitis acuta. Intumescent. et Tuberculosis glandularum retrobronchial. Ulcera tuberculosa tonsillæ et intestini ilei; Tuberculosis peritonei.

In the upper lobe of the left lung about 6 cavities with smooth walls, varying in size from a pea to a bean; the walls of the cavity were thin, sacculated, showed a caseous covering, and in a larger one situated longitudinally, a peribronchitic cavity, there was a cheesy mass; the pulmonary tissue between was permeated by tubercular nodules, miliary to submiliary in size, which were, however, quite few in number; this was moderately hyperemic but quite moist. At the right apex a cavity about the size of a nut, of similar construction, in a delicate air-containing portion of the parenchyma. In the anterior portions of the right, upper middle lobe, lobular jelly-like masses, and in individual areas caseation the size of a pea with adjoining edematous pulmonary substance and in the middle portions peribronchitic obliterating areas besides miliary and submiliary tubercles in small amounts.

Prof. Kretz added as an explanation: The condition was one of phthisis florida depending upon recent lobular bronchopneumonic foci in the upper lobe, no signs of an old obsolescent pulmonary tuberculosis. No especial induration but early desquamation and softening of the caseous masses in large portions. Some of the miliary tubercles are certainly younger than the older cavities.

The bacteriologic examination of the lungs in the cadaver shows profuse colonies of influenza bacilli besides streptococci in the cavities (and the unknown bacillus); in the antrum of Highmore in the choanæ and in the pleural exudate no influenza bacilli, only isolated colonies of the staphylococcus albus.

The case probably proves in a most pronounced manner how an extremely mild tuberculosis of the lungs with which the patient was affected and which was entirely without symptoms progresses rapidly due to an intercurrent acute infection from influenza bacilli and streptococci, how the influenza bacilli prepare the soil for the tubercle bacillus from which the latter conjointly with the former display their deleterious activity in the most disastrous manner. It is probable that the patient would have lived for years and years provided infection by influenza bacilli had not taken place and would have been able to sustain the tuberculosis of the lungs without symptoms until old age had

been reached! The fact that no old tubercular processes but only relatively fresh cavities—besides still more recent tubercular changes—were present in the lungs and that these cavities developed from a bronchopneumonic focus and that streptococci with profuse quantities of influenza bacilli were found in them, can probably only be explained in that the changes were the joint labor of the influenza bacilli (besides streptococci) and of the tubercle bacilli, the former preparing the soil for the latter. The patient died of an acute tubercle bacillus and influenza bacillus mixed infection, in which from the onset, the clinical character of the influenza infection was typically expressed and dominated the pathological picture, which resembled a severe intoxication throughout.

I desire to briefly call attention to one point in the clinical picture which I wish to utilize later on, viz., the phenomenon that at the acme of the disease during a period in which influenza bacilli were present in profuse amounts in the sputum the number of leukocytes—to make this absolutely certain they were counted by two persons from two different pipettes—only amounted to 5,000 per cmm.

From a bacteriological standpoint, I regard two factors as especially worthy of mention, first, the fact that immediately from the onset of the disease influenza bacilli could be determined in large amounts in the nasal secretion during a period in which the sputum was still free from these pathologic bacteria. I mention this expressly because Finkler¹ seven years ago stated that it was very probable that in an influenza infection of the bronchi, that is to say, of the lungs, at least in most cases, the infection starts in the upper portion of the respiratory passages and travels downward; “the strict proof of this is still wanting that in the onset of such an affection influenza bacilli are present upon the mucous membrane of the nose or of the pharynx.” I am not aware that this proof has been furnished from bedside experience by anyone else in the intervening period. For this reason I emphasize this finding which I obtained from my patient as an irrefutable proof that the infection unquestionably began in the nose and progressed in a downward direction. It is not without interest that in spite of influenza bacilli having been found *intra vitam* in the nose, that in the cadaver neither in the nose nor in the accessory cavities has Pfeiffer’s bacillus been determined—a proof for the well-known fact that the marked trigeminus pains are not always an expression of an infection of the accessory cavities but that they may also be due to simple toxic infectious neuralgias. The second factor to which I wish to direct special attention is the numerical proportion of the influenza bacilli and tubercle bacilli found in the sputum. It appears to me to be especially interesting that Koch’s bacilli could at first only be demonstrated in very sparse, later in somewhat larger numbers, whereas the influenza bacilli were mostly present in great numbers in the sputum. I consider this bacteriologic finding to furnish another confirmation of the thought which arose by reason of the clinical picture, that at least for the origin of the first part in the course of the disease, influenza played the chief rôle, tuberculosis only a secondary part. The quiescent tubercle bacilli were awakened by the invading

¹ *Finkler, loc. cit.*

influenza bacilli who were eager for strife, and after they were once stirred up they advanced and caused a fearful onslaught. Victory was assured on account of their united strength.

I recently had an opportunity of observing in the hospital, a case of mixed infection due to influenza and tuberculosis of the lungs which was almost the counterpart of the above-described and detailed case. Both cases are striking proofs that influenza although not producing deleterious effects in many patients that suffer from slight or moderate tuberculosis, may even in these bring about a fatal termination as well as in the severe tuberculous patient who is near the grave.

This category also embraces those cases in which an acute influenza affection and an exclusive acute miliary tuberculosis of the lungs occur together and rapidly lead to a fatal termination (in about eight to fourteen days). I have observed three cases of this kind, one during my service in the hospital and two in my private practice. In two of these three cases the influenza manifested itself in the form of an acute tracheobronchitis with lobular pneumonic areas of varying situation, in the third as an influenza bronchitis lasting for two years, showing muco-purulent sputum which always contained profuse amounts of influenza bacilli. These were found in one of the cases also in the cadaver, at the base of the lung between the miliary tubercular nodules and the lobular pneumonic foci in pure culture—no autopsy was obtainable in the other two cases. With the two other cases the diagnosis of miliary tuberculosis was made and was assured by the existence of choroid tubercles.

The above cases refer to the combination of influenza with pulmonary tuberculosis. However, it is not this affection alone in which endemic influenza is observed as a clinically important combination which even dominates the clinical picture, but in this respect our acute infectious diseases must be considered, above all.

The front rank among these is occupied by the acute exanthemata which quite frequently, as some recent books teach us, associate themselves with an influenza infection of the respiratory tract. I am sorry to state that I am without any personal experience in this respect, and, as to the investigation of others, which, besides, are very sparse, they concern themselves much more with the bacteriological determination of the combination than with the clinical aspect. As early as 1899, Paltauf¹ reported two cases of measles in which he was able to demonstrate in the cadaver influenza bacilli in the bronchi. Two years later Jehle² published a very elaborate and valuable article in which he came to the conclusion, above all, that in measles, as well as in scarlatina, an influenza of the respiratory tract (and that mostly in the lower portions of the same, sometimes only in the tonsils) represents a relatively frequent combination and most probably renders the course of the above-named acute exanthem considerably more severe. Also, according to Jehle, only in the acute exanthemata in particular, does an entrance of the

¹ Paltauf, *loc. cit.*

² Jehle, Ueber die Rolle der Influenza als Mischinfection bei den exanthematischen Erkrankungen und das Vorkommen von Influenzabacillen im Blute. *Zeitschr. f. Heilkunde*, Bd. xxii (N. F., Bd. ii), Jahrg., 1901.

influenza bacilli occur from the tonsils into the blood stream, thus causing bacteriemia and, thereby, the development of the severest metastatic processes (pleurisy, endocarditis, pericarditis, abscesses of the brain). Still another article, that of Süsswein,¹ treats of the occurrence of influenza bacilli in measles. This author—who, however, had an opportunity to satisfy himself of the presence of bacteriemia *intra vitam*—was able to determine the frequent occurrence of influenza in morbilli. He, too, considers influenza as a dangerous complication of measles, exerting an unfavorable influence. He reports the following in a clinical respect: “The fever, which in normal measles disappears completely on the second to the fourth day after the eruption of the exanthem, persisted for some time and was occasionally quite high, as will be noted from the temperature charts which registered 102.2° F. A more or less severe bronchitis was regularly present, which in some instances was combined with bronchopneumonia and pleurisy. The children became very weak and cyanotic, with superficial and accelerated respiration; the pulse was small and frequent. Tumor of the spleen was also demonstrable in some instances.” However, Süsswein emphasizes particularly, in contrast to the above, that there are also cases of measles influenza which clinically cannot be distinguished from uncomplicated measles.

Jehle² was also able, the same as in measles and scarlatina, to find influenza bacilli in the bronchi and in the blood of cadavers of patients that had died of varicella.

Not much more than we know of the relations between influenza and the acute exanthemata, are we acquainted with those between influenza, on the one hand, and diphtheria and pertussis, on the other. Here, also, it is the merit of Jehle to have determined the bacteriological fact that the above diseases frequently become associated—in pertussis Jehle even found influenza bacilli in the bronchi of all cases examined—however, without entrance of the influenza bacilli into the blood in these diseases. Jehle’s article was confirmed in regard to diphtheria by Leiner³ and this author as well as Jehle arrived at the conclusion that influenza forms a severe, even fatal complication of diphtheria. Other clinical studies are wanting so that in this particular domain of clinical medicine a large field is open to cultivation which, however, may not yield the results expected.

It is absolutely superfluous to state that all the above-mentioned facts are of the greatest importance from a hygienic standpoint; for great caution must be exercised in that all cases of influenza occurring in pertussis, measles, scarlet fever and varicella should be strictly isolated from such cases in which this complication does not occur; this requirement is also justified in cases in which influenza and tuberculosis occur together. Every case in which complication occurs indicates a severe, eventually fatal, danger for the uncomplicated adjacent case. If we omit, as is readily conceivable, the isolated and sporadic cases of influenza occurring in other diseases—for example carcinoma, nephritis, which after all suggest nothing but what is obvious, namely

¹ Süsswein, *Influenza bei Masern.* Wiener klin. Wochenschr., 1901.

² Jehle, *loc. cit.*

³ Leiner, *Ueber Influenza als Mischinfection bei Diphtherie.* Wiener klin. Wochenschr., Nr. 41, 1901.

that after influenza has once become endemic it is quite apt to occur as a complication in other diseases, there remains only the discussion of one more combination of diseases, that of influenza and enteric fever.

With this special theme I enter upon a realm of science that up to this time has not at all been scientifically investigated. It is true a few observations exist which, at least in part, refer to the subject under discussion, thus, for instance, Anders¹ who up to 1896 reported five cases in which enteric fever occurred as a subsequent complication of influenza. Anders finds that the statistics of influenza epidemics confirm the fact that an organism weakened by grippe is much more susceptible to infection by enteric fever than otherwise. Whereas therefore, Anders only treats of the supervention of typhoid fever upon influenza most of the other authors who refer to the relations of enteric fever and influenza mention nothing but the differential diagnosis between the two affections which, according to some, can be established with absolute certainty, whereas others consider it very difficult at times. I find only one author, Graves,² who refers to influenza as a complication of enteric fever. This author states, according to Biermer, that "Influenza never occurs as a complication of enteric fever, but, however, upon the day on which a favorable defervescence occurs, patients become susceptible to influenza and not infrequently are infected." "Confirmations of these observations"—are added by Biermer in his classic monograph upon influenza—"we have not found in literature." Neither have I found this question referred to until 1901 although a long period of time had elapsed since this statement of Biermer when Babes and Robin³ published an article upon associated epidemics. They report eight cases—from two epidemics occurring in different localities—in which they found influenza bacilli in the sputum or in the respiratory passages at the autopsy. In most of the cases Widal's serum reaction was positive. Nevertheless, these authors are not in position, for very positive reasons, to denote these cases as atypical grippe or to assume with certainty that the cases represent a complication of grippe with abortive enteric fever. But they assume under all circumstances that their cases demonstrate that "it is not sufficient to find the Pfeiffer bacillus during an epidemic in order to maintain that we are dealing with influenza or a positive serum reaction to declare that enteric fever is present; it is possible to encounter simultaneously one or the other of these diagnostic elements in the course of the special symptom-complex in associated epidemics the case being neither grippe nor enteric fever" (*qui n'est pas la grippe et qui n'est pas non plus la dothienterie*).

This work, therefore, calls attention to the possibility of a combination of a simultaneous, or even epidemic, appearance of grippe and enteric fever directly, although absolute certainty regarding an existence of a combination of these two diseases has not been proven as yet.

It was not until quite recently that it was determined with certainty that influenza bacilli occur in the sputum in enteric fever, that is to say in the

¹ Anders, Typhoid fever as a complication and a sequel of Influenza. Philadelphia Reporter, vol. lxxiv, Med. News, 73, quoted from *Virchow's Jahresbericht*, 1896.

² Graves quoted by Biermer, *loc. cit.*

³ Babes et Robin, Les épidémies associées. La Semaine médicale, 42, 901.

bronchial secretions, even that typhoid bacilli and influenza bacilli have been found side by side. Jehle¹ who in his investigations upon typhoid bacilli in the sputum of enteric fever was the first to call attention to this fact from a bacteriological standpoint. "Typhoid bacilli may occur in pure culture as well as in association with other micro-organisms, especially with the bacillus of influenza."

However, this most interesting bacteriological finding naturally suggests the question which I believe to be quite proper: Were all the individuals in whose sputum typhoid bacilli and influenza bacilli have been found actually attacked by enteric fever and influenza or were the latter micro-organisms only of subordinate significance or entirely irrelevant to the occurrence of the pathological picture? I believe this question to be fully justified, not that I consider the bacillus of Pfeiffer, as does Rosenthal,² to be a simple saprophyte of the air-passages, but because there are normal hosts of influenza bacilli as well as diseased ones who are, however, affected by another malady than influenza. Jehle does not answer this question and this is quite obvious as he is dealing with an entirely different phase, namely that of finding the typhoid bacilli in the sputum of patients affected by enteric fever. Nor did he have an insight into the clinical course of the cases and as the characteristic changes in the lungs at the autopsy due to the influenza bacillus were not found—this knowledge I owe to a verbal communication of Dr. Jehle, through Prof. Kretz,—I desire to leave the question open: Whether in the cases observed by Jehle enteric fever was actually associated with influenza or not?

To solve this question I shall quote the history of one of my patients:

L. K., aged twenty-three, clerk, admitted November 7, 1901, discharged January 20, 1902.

History.—The patient had always been healthy with the exception of a tendency to constipation. At the beginning of November (All Saints' Day), pains occurred in the throat upon swallowing, soon followed by chills, high fever; very marked headache which was localized to the frontal region, great lassitude and prostration, loss of appetite, marked muscular pains especially of the lower extremities, particularly upon pressure. The pains upon deglutition and the headache improved, the other pathological symptoms, however, persisted and caused the patient to come to the hospital.

Status Præsens.—November 7th: Temperature remittent, from 101.3° F. to 105.3° F., consciousness undisturbed even at night; conjunctivæ markedly injected. Tremor of the tongue was present, the organ was dry in the centre and fissured; the papillæ of the tip were swollen to the size of a pin-head and were red. There were marked pains in the fossæ caninæ upon pressure. Pressure upon the tragus of both sides was also painful. It appeared remarkable that a pressure upon the trachea in the jugular fossa apparently caused great pain. Over the lungs, showing normal percussion, there was coarse breathing everywhere, and a conspicuously profuse diffuse catarrh which showed consolidation toward the base, the râles were partly dry, partly moist. No sputum. The heart showed nothing abnormal, pulse 88 to 120, no diastolic murmurs, respirations 28 to 30, very slight meteorism was present, no roseola; the right kidney was palpable, but the spleen was not, and could not be demonstrated upon percussion. The ileo-cecal region was sensitive to pressure, distinct gurgling. The muscles of the calves of the legs were very sensitive to pressure. The urine showed traces of albumin, the diazo-reaction was decidedly positive.

¹ *Jehle*, Ueber den Nachweis von Typhusbacillen im Sputum Typhuskranker. Wiener klin. Wochenschr., Nr. 9, 1901.

² *Rosenthal*, loc. cit.

November 8th to 14th: Continued remittent fever, minimum temperature 100.6° F., the maximum afternoon temperature 104.2° F., the clinical picture unchanged, only the pulse showed a tendency to dicrotism. The pulse frequency compared to the temperature was always low, about 100. Conspicuous variation between the pulse in the recumbent posture and while sitting up, the difference in countings amounting to about 20 beats, respiration never above 28. During the first three days five non-characteristic fluid evacuations, followed by four and then three diarrheic stools; the sputum was sparse, mucoid. Number of leukocytes (November 11th), 7,600.

November 15th to 17th: Spleen distinctly palpable, temperature conditions unchanged, the maximum being 104.9° F.; catarrh is decided, diffuse, tongue reddened upon the borders and in the centre, in between showing a slight whitish coat, papillæ enlarged (like the tongue in enteric fever), the pulse distinctly dicrotic. Persistent diarrhea present.

November 18th to 21st: Distinct remissions in the temperature, from 99.9° F. to 103.3° F., later from 99.8° F. to 102° F.; the pulse fluctuated between 88 and 100; marked sweating.

November 22d to 23d: Bronchitis unchanged, continued fall in temperature (97.9° F. to 100.2° F.). Pulse 84, diuresis amounting to 1,400 c.c.; sweating.

November 24th to 30th: The bronchitis, though showing slight improvement, still marked. Râles were noted after coughing, they were diffuse, dry and moist, medium to fine without having metallic quality. The temperature on November 25th was again 99.5° F., otherwise subnormal. The diarrhea had ceased and the spleen was no longer palpable, the sputum was sparse, no longer mucoid.

December 1st to 11th: A remittent rise in temperature, acme 104.7° F., followed in the succeeding days by defervescence; objective findings with the exceptions of signs of catarrh, are negative, maximum of the pulse 100. Number of leukocytes December 7th, 7,800; on December 6th, 9,600.

December 12th: Normal temperature, post infectious bradycardia and polyuria. Convalescence interrupted by a temporary rise in temperature, recovery very gradual.

Gruber-Widal serum reaction: November 8th, 1: 20, positive in five minutes, 1: 50 negative; November 15th, 1: 200 prompt, 1: 500 negative; December 3d, 1: 100 prompt, 1: 200 in one-half hour, 1: 500 negative; December 11th, 1: 20 prompt, 1: 100 in one hour, 1: 200 negative.

Sputum: November 8th, profuse quantities of influenza bacilli colonies, no typhoid bacilli. November 25th, great numbers of influenza bacilli besides staphylococcus albus and aureus.

Urine negative bacteriologically.

To recapitulate, we were unquestionably dealing with an infectious disease, first lasting four weeks with a subsequent recurrent rise of temperature lasting twelve days. The first stage of four weeks was distinguished by an onset with chill and high temperature amounting to 104.9° F., a relatively slow pulse which in the course of the affection became distinctly dicrotic, a Widal reaction which was at first feebly positive, later well developed (1: 200), and which gradually diminished during defervescence, distinct enlargement of the spleen, first leukocytosis (15,000), followed by slight leukopenia to 7,600, which during the relapse, after a temporary increase in the number of leukocytes again became noticeable. With the decline in temperature a tendency to sweating appeared; a positive diazo-reaction, ileo-cecal gurgling and pain, diffuse bronchitis phenomena.

In consideration of all these factors, it was probably clinically necessary to make a positive diagnosis of enteric fever, although the onset of the disease with chill is not a common condition and because leukocytosis was present at first and the subsequent leukopenia was not marked. However, the remarkably intense and extensive bronchitis was very surprising from the onset. We

are accustomed in the diagnosis of an uncomplicated case of enteric fever to regard as particularly valuable the parallelism between the important symptoms (bronchitis, splenic tumor, cerebral symptoms, meteorism, course of the temperature, etc.) and were very much surprised from the onset of the disease by the exceptional conditions in our case. The bronchitis was too pronounced, for a medium attack of enteric fever in proportion to the other symptoms and, what was to some extent remarkable, was the fact that the bronchitis persisted considerably longer than the other typhoid manifestations. An explanation for this condition was found in the examination of the sputum which revealed the presence of numerous influenza bacilli. There can scarcely be a doubt that these bacilli did not play a secondary part in the case described above but were present as virulent pathogenic organisms and this we were taught by the fate of a second patient who attacked by typical enteric fever was in the same room in an adjoining bed to the patient whose history has just been detailed. This second patient had already passed through a medium severe and unquestioned attack of enteric fever (eruption, Widal reaction, at first prompt in a dilution of 1:40, then in the further course prompt 1:100, complete in about five minutes in 1:200—leukopenia, etc.), when, after the disease had lasted for five weeks, almost after complete defervescence (maximum temperature 100° F.), the patient again showed fever (temperature 104.2° F.), definite defervescence occurring only a month after this renewed attack, which clinically ran its course with the symptoms of an extensive bronchitis. Repeated examinations of the sputum of this patient during the second period of this disease showed large numbers of pure cultures of influenza bacilli.

There is probably no doubt that this second patient with enteric fever had become infected with influenza from the first patient. This case, therefore, proved that a simultaneous influenza infection was present with typhoid infection in the first enteric fever patient also. It further proves that enteric fever and influenza may coexist at one and the same time, which up to then had not been demonstrated clinically. We were able to determine this combination of diseases in another case.

R. E., aged nine, school girl, admitted to the hospital February 8, 1902, discharged but not cured, April 17, 1902.

History.—She had been well all her life with the exception of measles. Her present affection commenced about a week previous to admission, with general symptoms, loss of appetite, apathy, alternating sensation of heat and cold, prostration, diarrhea, followed by constipation. The father of the child, three weeks before the beginning of the disease in the child, had been discharged cured of enteric fever from another hospital.

Status Præsens.—February 19th: Consciousness clear, at night slightly disturbed; no headache, great prostration. Herpes corneæ in the right eye, lips dry, tongue moist, point not coated, papillæ slightly reddened. Cyanosis of moderate degree. Over both lungs, besides puerile respiration, very dense either dry or moist, medium to fine râles, decreasing in intensity from below up, slight tympanitic note over the lower portions of the lungs, especially on the right. Nothing abnormal was noted in the heart, and no distinct diastolic murmur of the pulse. The abdomen showed slight meteorism and numerous hemorrhagic flea bites; the spleen extended one finger breadth below the border of the costal arch. Ileo-cecal region was without pain, no gurgling. No pains at the points of exit of the trigeminus and no muscular sensitiveness to pressure. The diazo-reaction was very slightly positive, the sputum was sparse, muco-purulent and streaked with

fresh blood striæ. The temperature was remittent, to 102.7° F., the pulse frequency 116, respiration 24.

February 20th to 24th: With remittent temperature to 102.6° F., continuous very intense catarrh at some areas, especially in the right scapular angle, with slight tympanic note in this region, very dense, with fine râles without increase of vocal resonance. Continued cyanosis of the lips and cheeks, herpes corneæ healing. The number of leukocytes was 3,200.

February 25th to 28th: Tendency to perspiration; catarrh the same as before. The spleen could still be palpated one-half finger breadth below the costal arch, diminishing in size; cyanosis was still present. The sputum was very sparse, muco-purulent, remarkably viscid; very violent cough. The temperature on February 24th showed a maximum of only 100.6° F. and from February 25th on permanently subnormal. Pulse frequency 116 to 120; number of leukocytes on February 27th was 7,200.

March 1st: Profuse perspiration, catarrh had almost entirely disappeared, the cyanosis still persisted.

March 2d to 6th: The catarrh had diminished so much that only isolated râles could be noted at the base on the right with otherwise normal percussion sounds all over. Temperature permanently normal.

March 7th to 20th: Well-being with absolutely normal temperature. Objectively normal conditions, only the spleen still one-half a finger breadth below the costal arch; the number of leukocytes now amounts to 5,000.

March 21st: A rise of temperature to 99.5° F. occurred.

March 22d to 27th: The temperature rose to 103° F., on the following day to 104.2° F., at which height it remained almost continuously. Pulse 132, respirations 126; only very isolated basic catarrh. The spleen was unchanged; no dirotism. The patient was in relatively good health. Number of leukocytes 3,100, diazo-reaction positive.

March 28th: Over the right lung posteriorly partly moist partly dry catarrh, most profuse in the right axilla. Epistaxis. The tongue was not of the typhoid character. Some roseola noted on the abdomen near the right costal arch, and on the right side. The temperature remained continuously at 104.3° F.

March 29th: Numerous roseola on the trunk posteriorly and anteriorly; no dirotism. Diffuse moist and dry catarrh on both sides. Sparse cough, mucus sputum. The temperature fluctuating between 100.9° F. and 102.4° F., pulse 115.

March 30th: Roseolar eruption fading; a culture from the same had remained sterile (not elaborated after Neufeld), temperature diminishing, remittent to 102° F.

March 31st to April 2d: Remittent fever continues, temperature to 101.7° F.; the stools were compact, formed. Catarrh rapidly decreasing, only very sparse especially in the right lower and middle lobes.

April 3d to 5th: Leukocytes 4,000, the spleen unchanged, pulse frequency considerably diminished, the spleen was still one-half finger breadth below the costal arch. The catarrh had disappeared almost entirely, except posteriorly at the base; the temperature was subnormal.

April 6th to 13th: Absolute well-being; normal temperature. Spleen unchanged. Condition of the lungs normal.

April 14th: Remittent fever with evening temperatures up to 102.9° F., subjective condition scarcely disturbed; no exanthem; tongue moist, coated. No bronchitis.

April 15th to 17th: The spleen increasing considerably in size; number of leukocytes, 2,700; diazo-reaction negative; fever remittent; formed stools.

The patient was discharged at the request of her parents.

Sputum examinations: February 21st, diplococcus lanceolatus colonies and streptococci; no influenza bacilli. February 24th, numerous colonies of influenza bacilli, besides diplococci and streptococci. February 28th, especially numerous colonies of influenza bacilli, with isolated streptococci. March 28th, especially numerous colonies of influenza bacilli, besides streptococci; numerous staphylococcus aureus but no typhoid bacilli.

Widal reaction: February 19th, 1:20, positive. February 27th, 1:100, complete in one and one-half hours. March 14th, 1:20 in about ten minutes, 1:50 in three-quarters of an hour; 1:100 complete in one and one-half hours.

When I saw the patient on the first day I had come to the conclusion, in view of the extensive bronchitis, of the marked cyanosis and of the other conditions, that a pure enteric fever was probably not present, but I wavered between a typhoid infection which might be associated with an infectious process of a different nature in the bronchi (I thought first of influenza, also of streptococcus infection of a subdiaphragmatic localization, the latter especially in remembrance of three cases of enteric fever which I had also seen at the clinic, and which all began with a pleurisy, and in which, as was confirmed by the autopsy, the latter condition was due to the streptococcus pyogenes, in which, therefore, a typhoid-streptococcus infection had simultaneously taken place from the onset), between miliary tuberculosis and influenza, or of a streptococcus infection with a pseudotyphoid picture. The further course of the disease, the Widal reaction, the condition of the leukocytes, the appearance of the eruption, in spite of the negative result of the examination of the blood from the roseola, removed all doubts regarding the diagnosis of enteric fever, although the abnormally rapid rise and fall of the temperature in the second relapse, third attack, appeared rather strange to me. However, the examination of the sputum confirmed my assumption also in the other direction in that we were dealing, not with a pure type of enteric fever, but with enteric fever and influenza. I desire again to call attention to the fact that I, from a purely clinical viewpoint, considered this diagnosis to be probable from the onset, because I again had called particular attention to the contrast between the severe bronchitis and the cyanosis, on the one hand, and the relatively slightly developed typhoid symptoms, on the other hand.

Apart from the fact that these three cases furnish the absolute proof of the coexistence of enteric fever and influenza, also clinically they teach us still more.

The second case proves that a renewed rise of temperature of several days' duration, after the typhoid affection had completely run its course, does not signify only a recurrence of this disease, that is, an abnormal localization of the typhoid bacillus, for instance in the bones, a secondary bacterium coli infection or a secondary suppurative process, for instance originating from the oral cavity, but that such a rise of temperature may also be due to a post-current influenza infection.

The above three cases demonstrate, further, that the Widal reaction in enteric fever, immaterial (first and third cases) whether it is still at its height or whether it has to the greater part run its course, is not suppressed or attenuated (1:200 positive) by a concomitant influenza infection, that, therefore, no analogous conditions are created thereby as may be caused, as is well known, by intercurrent pneumonias or by jaundice in enteric fever.

One fact appeared remarkable to me in the first two cases, namely, the relatively insignificant leukopenia during the simultaneous influenza infection, which, in the first case, permitted a decrease of the leukocytes to only 7,600, in the second case—which, it is true, is less applicable in this respect—to 8,000. It might be surmised that influenza, therefore, is able, to a certain extent, to prevent the reduction in the number of leukocytes, which is of such importance in the diagnosis of enteric fever, so much more so as in our

first patient 15,000 leukocytes were counted at the onset. However, with regard to our third patient, we must do away with this supposition or, at least we must restrict it very materially. It may be that an influence upon the typhoid blood-picture is exerted by a concomitant influenza, in the sense of a restriction of the leukopenia, in some cases; however, this contention is not correct in all instances. In contra-distinction to this, I desire once more to call attention to the fact that the number of leukocytes in a case of my own observation of acute influenza and pulmonary tuberculosis was only 5,000. This opens up the road for further studies.

All three cases, finally, confirm most conspicuously that the above-quoted words of Babes and Robin, rendered in abbreviated modification, are undoubtedly correct. We may maintain: The most pronounced Widal reaction does not prove as yet that enteric fever alone is at the bottom of the pathological picture. The demonstration of Pfeiffer's bacilli in the sputum, even in pure culture, does not prove as yet that influenza alone is at the bottom of the pathological picture, even if we well know that a typhoid-like course of influenza exists. For there are cases in which typhoid fever and influenza are simultaneously present side by side.

In consideration of such cases we encounter, as we have seen, very considerable diagnostic difficulties. They compel us to use a greater exercise of our diagnostic skill, to found our diagnostic art upon a broader basis. For they again teach that not one disease alone, but several of them, attack man, they bear witness of the existence of combinations of diseases as acknowledged elsewhere. To unravel them diagnostically is an art which is quite as difficult as it is agreeable and of practical value. To practise it successfully we require thorough study in the clinic of each individual affection, the calling upon all auxiliary sciences, the knowledge of which no specialist must master more profoundly and more thoroughly than the clinician. His field of knowledge is necessarily a broad one; so much more beautiful is his art which investigates whatever promises to prove advantageous, holding that which it can utilize. It may consider as one of its most important aids, the youngest of our medical auxiliary sciences, bacteriology. Without the latter, we would not have been able to determine what new and known facts are contained in the above. Thanks to the same, I may conclude with the following words:

Influenza has come to be fully acknowledged as an epidemic disease; it should quite as much be recognized as an endemic and as a sporadic affection.

MALARIAL DISEASES

By F. LÖFFLER, GREIFSWALD

HISTORICAL REVIEW

At the dawn of the new century, in surveying the acquisitions due to medical research for the benefit of mankind, we must acknowledge that among them, one of the most practical and most significant was the elucidation of the origin, distribution and successful combat of that group of diseases which is the most widely disseminated of all the infectious diseases, viz., malaria.

These diseases are the ones which force man to purchase habitation in the most profitable portions of the world which nature has endowed with most luxurious vegetation, by a great sacrifice of life and health on his part; the diseases of tropics actually paralyze civilizing factors in vast districts. These diseases, further, play the most conspicuous part in the pathology of tropical and subtropical countries and impress upon these regions their specific stamp. These affections have been designated by the most varied names for they have been known since antiquity. The periodical appearance of the fever, with afebrile pauses between the attacks, has always been most remarkable to physicians.

Typorum et periodorum febrilium miracula vidit omnis ætas et obstipuit, videbit omnis posteritas, posteritas forsan omnis obstupescet” is remarked by one of the most thorough students of this group of diseases, Werlhof.

Hippocrates, in whose works the professional knowledge of the ancients is faithfully transmitted to us, has strictly separated this fever group as quotidian—tertian—and quartan fevers from numerous other fevers, such as inflammatory fever, continued fever, etc.

On account of the peculiarity of the fever type, these fevers have been designated as intermittent fever and as remittent fever. According to the regions in which it develops, it has been called swamp fever, paludism, and, on account of its supposed causative agent, the unsanitary condition of the air, it has been designated malarial fever.

These diseases have been observed over the entire inhabited earth.

GEOGRAPHICAL DISTRIBUTION OF MALARIAL DISEASES

Hirsch, in his great historico-geographic pathology, has exhaustively described the geographical distribution of malarial diseases.

In general, the affection shows a decrease in extent and in intensity which progressively increases from the equator to the poles, up to a certain limit,

beyond which it no longer appears either endemically nor epidemically. This boundary is represented by a line which begins in the western part of North America at about the 55th degree north and extends to the 45th degree in the eastern part, then in Europe rising again in Sweden and Finland at the 63d to the 64th degrees north and terminating in Northern Asia above the 55th degree north.

The southern boundary is not quite as extensive, reaching, at most, only to the 35th degree south. The isotherm of 15° to 16° C. upon the whole designates the boundary limit for the occurrence of malaria.

ENDEMIC MALARIA

In Africa, malaria prevails along the entire tropical west and east coasts, being especially intense in the areas traversed by the Senegal, Gambia, Niger, the Gabun, and Kamerun Rivers, along the entire western coast down to the Congo. Further south, the intensity of the disease declines. Cape Colony is almost free from the disease as is also the Island of St. Helena. Upon the eastern coast, the affection flourishes from Delagoa Bay to entire German East Africa as far as the River Tana. The coast region of the Red Sea, especially Massowah, further Abyssinia, the Soudan and Lower Egypt, is rich in malaria. The islands adjacent to Africa, Madagascar, Réunion and Mauritius, are intensely malarial, the latter island only since 1866. The northern coast of Africa, especially Tripoli, Tunis and Algiers, show a marked preference for the disease.

Extensive fever districts are found upon the shores of the Mediterranean. In Italy, the plains of the Po, and then the entire west coast from the mouth of the Arno, with its swamp, down to Calabria, especially the Tuscan Maremmes, the plains of Grosseto, the notorious Roman Campagna, the Pontine swamps, the swamp of Capua, further Sicily, Sardinia, and Corsica, are intensely malarial. The coast regions of Istria, Dalmatia, Albania, numerous regions in Greece, the Ionian Islands, the shores of the sea of Marmora, the western and southern coasts of Asia Minor, the Syrian coast cities, the valleys of the Lebanon, the valley of the Jordan, further, also the Islands, especially Crete, are malarial.

The mouth of the Rhone represents the malarial district of the French coast.

The southern and western coasts of Spain, the swampy shore of the Guadiana and Guadalquivir and the low lands of the Tagus, further, the flat coast of Granada and Murcia, Barcelona and Valencia are implicated as also are the highlands of Castile and Estremadura, Galicia, and Asturia. Gibraltar enjoys an especial immunity.

In France, outside of the southern portions, especially the west coast is malarial, the lower regions of the Loire, the district of Sologne and the notorious swampy plain of the Brenne are to be particularly named; further, Vendée, the Gironde, the plains of Landes and the coasts, of Languedoc and Provence which abound in lakes and swamps.

In Switzerland, the disease only occurs in the southern portions of the Canton of Tessin and upon the shores of the Rhone in the Canton of Wallis.

Extensive malarial districts exist upon the Belgian west coast, western and eastern Flanders, extending over the Netherlands, especially Groningen, Friesland, Zeeland, Drenthe, and Overijssel; further, the marshy districts of Friesland and Oldenburg, Dittmarschen, the west coast of Holstein and Sleswick; formerly, the entire Baltic coast of Mecklenburg, Pomerania and East Prussia, were malarial, but the affection no longer exists in these districts. The Rhine and its tributaries, Westphalia, some parts of the Harz, of the Margravate Brandenburg and the Province of Posen were formerly intensely malarial; the disease has entirely disappeared from these countries. In southern Germany, where malaria prevailed intensely in the regions of the Rhine and the Danube with their tributaries, it disappeared decades ago.

Great Britain is now free from malaria, formerly especially the eastern regions, those situated about the Wash, the districts known as the "Fens," the districts surrounding the mouth of the Thames, as well as the coast of Scotland, were malarial, as is shown by the exhaustive investigations of Nuttall, Cobbett and Strangeways-Pigg.

In Denmark, which was previously intensely malarial, the affection only occurs now in the Islands of Laaland and Falster.

Norway is practically free; in Sweden, the affection exists upon the coasts of the great lakes, Lake Malar and Lake Wener, and upon the eastern coasts, at the mouths of the coast streams Angermann-Elf, Dal-Elf and Götha-Elf.

The great plains of the Danube are mighty malarial regions. The March-field, the small and great Hungarian Plains where the affection has always ranged as Dacian and Pannonian fever, furthermore in the swampy districts of Croatia, Servia, Montenegro, the river plains of Wallachia (especially in the Dobrudja) and Bulgaria and the valleys of Moldau. The endemic malarial regions of European Russia are the Crimea, the river regions of the Don, Dnieper and Dniester, the shores of the Volga, the Caucasian Plain, further, the swampy plains of Western Russia, Orenburg, Samara, Kazan, the Russian Baltic provinces and Novgorod. In Poland the disease occurs in the lake regions; in Galicia only in the watery northern portions.

Whereas the south coast of the Black Sea is markedly malarial, the high plateau of Armenia and the central part of the Transcaucasia are almost entirely free.

Malaria is widely distributed in Persia, especially in the valleys of the Atrak and Gurgan, as well as upon the coasts of the Persian Gulf. Baluchistan and Afghanistan, and the river regions of the Indus and Ganges, especially Punjab, are intensely malarial. The disease prevails everywhere in India, thus in the presidencies of Bombay, Madras, Bengal and in the northwest provinces, the high Plateau of Deccan, with its so-called "hill fever," is notoriously malarial.

There is severe malaria in Ceylon.

In Farther India it is found everywhere and is especially marked in the richly irrigated plains of Siam and Cochin-China. The islands of the Indian Archipelago are intensely infested, particularly the coast regions of the same. This malarial region extends further southward as far as New Guinea which is notorious on account of its virulent malaria.

Australia, Tasmania, New Zealand and numerous oceanic island groups

show a conspicuous immunity to malaria. It is reported that the disease has only recently been introduced into New Caledonia. An intense malarial region is distributed on the Asiatic Continent in the tropical and subtropical areas of China into Corea. The complete immunity of Singapore is conspicuous. Siberia is free from the disease excepting a few districts such as Barnaul and the Steppes of Barabinsky which abound in swamps and salt lakes.

Japan, with the exception of a few coast cities, and the more southerly situated islands of Shikoku and Kiushiu, is free from malaria.

America has extensive malarial districts; primarily the Antilles are particularly implicated, but with some exceptions, such as Antigua, St. Vincent and Barbadoes; Bahama and Bermuda are entirely free. The eastern coast of South America, especially Guiana, with the notorious Cayenne, has very severe types.

In the northern part of Brazil, malaria is less intense but still quite extensive, whereas the southern countries, Uruguay and Argentine, enjoy an almost absolute immunity.

The coast of the Pacific Ocean was formerly free, but since 1851 severe epidemics have occurred. Peru has always been an intense malarial focus, as well as the coast of Ecuador and of Columbia.

The Atlantic coast of Central America is intensely malarial, the Pacific coast less so.

Mexico is malarial in the coast regions, especially along the Rio Grande del Norte. The high plateau, however, is free and the Pacific coast is only malarial to a slight extent.

North America shows a mighty malarial district along the Colorado, the Brazos and the Mississippi, only elevations of over 6,500 feet form the limit. Upon the great prairie ascending toward the Rocky Mountains malaria is only present in isolated districts. The sandy hilly zone of the state of Mississippi is free from the disease. Florida and Georgia are intensely malarial, as well as the coasts and the damp river borders of the Carolinas, Virginia and Maryland. In the middle states, and in Tennessee and Kentucky, there is but moderate malaria, it is more marked in the prairie states proper, Ohio, Indiana, Illinois, Missouri, Iowa, Minnesota, Wisconsin, and Michigan, gradually decreasing in intensity toward the northwest. The shores of the great lakes, particularly of Lake Ontario and Lake Erie are very malarial, whereas Lake Michigan and Lake Huron are free from the disease.

Malaria has declined greatly in the states of New York and Pennsylvania.

In the New England states it has almost disappeared. In Canada it is found up to the 44° and in Newfoundland up to the 46° north. Nova Scotia, New Brunswick and Greenland, as well as the Island of Spitzbergen, are free.

The western states of North America are malarial, particularly the valleys of the Rocky Mountains, where the disease is known as "Mountain fever"; this is particularly marked in Utah, Wyoming and Colorado, further, in the valleys of the Sacramento and the San Joaquin in California. [Several distinct diseases have been described under the designation mountain fever. Among them anchylostomiasis and enteric fever are especially important. Malarial fever is no longer considered under this name and in any doubtful case or group of cases the finding of the malarial parasite in the blood would

at once determine the diagnosis. It would simplify our nosology if such vague popular terms as mountain fever were abandoned. ED.] The disease also exists in Central Arizona, whereas the subtropical coast of California from Monterey to San Diego shows a remarkable immunity.

This brief review, compiled from Hirsch, shows that malaria is endemic in extended districts throughout the earth.

The history of malaria further teaches that occasionally severe epidemics have developed from these endemic regions, under favorable circumstances affecting large districts which ordinarily were entirely free from the disease. The affection has even occurred in the form of great pandemics, distributing itself over entire continents giving rise to phenomena which characterize the malarial diseases as true infectious diseases. Thus, according to Hirsch, pandemics have spread over entire Europe during the years 1557 and 1558, 1678 to 1682, 1718 to 1722, 1748 to 1750, 1770 to 1772, 1774 to 1783. The last century witnessed such great epidemics in 1806 in Northwestern Europe, in 1812 in Southern India; pandemics were noted, furthermore, during the years 1823 to 1827, 1845 to 1849, 1855 to 1860 and 1866 to 1872. After such epidemics a marked retardation of malaria has been observed even in its endemic regions.

It then frequently happened that it periodically became entirely extinct in previous endemic districts, this lasting for decades, thus in Holland, in the North German marshes and in many other regions of Northern Germany, in Denmark, Sweden and North America. On the other hand, the appearance of new endemic areas has been observed, especially upon Islands, as for example in Amboina in the Indian Archipelago, in Réunion and Mauritius, but also in Chile, in Virginia and Pennsylvania and in other regions of America. It appears that at present malaria is distributing itself over many of the Polynesian Islands which formerly were exempt; it seems also, according to reports of Schoo, from Krommenie in Northern Holland, and of Mühlens, in the marsh districts of the North Sea, that malaria after a long period of quiescence has reappeared, so that the disease which had almost entirely lost its former importance for Central Europe again commands particular interest in this part of the world.

ORIGIN OF THE FEVER

Physicians early endeavored to form a conception regarding the causes of this peculiar fever. According to the view of Hippocrates, most fevers originated from the bile. "The bile dominates the body during the summer and in the fall, black bile is present in large quantities during the autumn and is then most powerful. Daily fever now arises, besides the synochial fever due to abundant bile, and in comparison to the other fevers ceases most rapidly, but its duration, in comparison to the synochial, is the longer the less the quantity of the bile which gives rise to it, and, furthermore, because the body enjoys an intermission, whereas in the synochial fever there is not a momentary pause.

Tertian fever, however, is of longer duration than daily fever and is due to a smaller quantity of bile. The longer the period during which the body

enjoys an intermission, during the tertian fever, in comparison to the daily fever, the longer will this fever persist in comparison to the daily fever. The quartan fevers, finally, behave in all points exactly in the same manner, but they last longer than the tertian fevers and all the more so the slighter the quantity of bile which causes heat and the greater the quantity of this or that substance which cools the body in which the quartan fever participates. This surplus in the duration and the difficulty in its removal is caused by the black bile; for black bile is the most tenacious of all the juices in the body and persists for the longest period. That quartan fever is due to black bile, may be recognized from the following fact: In the late summer persons are mostly attacked by quartan fever, particularly those between the twenty-fifth and forty-fifth years of age, because, as is well known, particularly this period of life is governed by black bile, and the season of the late summer, above all, is in greatest sympathy with black bile. In all those who are attacked by quartan fever outside of this season and this age, it is known that the fever will not last long unless the affected individual is attacked by another disorder."

This view of Hippocrates prevailed with physicians for centuries and even in the course of time was not materially altered. The yellow and the black bile produced the fevers, that was certain; only the explanation of the causation of the different types gave rise to differences of opinion among physicians, and medical authors exhausted themselves in subtile explanations. It is not surprising, therefore, that a new conception regarding the nature of these fevers did not originate from physicians fettered by dogmatic scholastic medicine; but laymen who were not encumbered or prejudiced by the teachings of the Medicine of the Schools were intent upon interpreting certain observations from the practice of daily experience and they endeavored to draw practical conclusions from them.

Marcus Terentius Varro, the contemporary of Pompey and Cæsar, one of the greatest scholars of ancient Rome, prominent as a general and as an agriculturist, in his work upon agriculture, refers to the local conditions that are important in constructing a villa. He emphasizes the point that swampy localities should be avoided, he says: "*Advertendum etiam, si qua erunt loca palustria, et propter easdem causas et quod arescunt, crescunt animalia quædam minuta, quæ non possunt oculi consequi, et per æra intus in corpus per os ac nares perveniunt, atque efficiunt difficiles morbos.*" The villa should also be built upon high ground, "*in sublimi loco,*" a point at which it may be surrounded by fresh breezes and where the sun may shine upon it, "*quod et bestiolæ, si quæ prope nascuntur, aut inferuntur, aut efflantur, aut aritudine cito pereunt.*"

The same thought, that animals which give rise to diseases are produced by swamps was uttered about one hundred years later, about the middle of the third century by Columella, a contemporary of Celsus who was one of the most prominent agricultural authorities of antiquity. In his book "*De re rustica*" and likewise in a discussion regarding the construction of a villa and its surroundings, he says: "*Nec paludem quidem vicinam esse oportet ædificiis, nec junctam militarem viam, quod illa caloribus noxium virus eructat, et infestis aculeis armata gignit animalia, quæ in nos densissimis examinibus*

involutant; tum etiam nantium serpentiumque pestes, hiberna destitutas uligine, cœno et fermentata colluvie venenatas emittit, ex quibus sæpe contrahuntur cæci morbi, quorum causas ne medici quidem perspicere queunt."

A somewhat different conception of the deleterious effects of swamp air was given by the military constructor of Cæsar and Augustus, Vitruvius, who does not ascribe the noxiousness to the direct action of the animals living in swamps upon man, but to the air which is poisoned by the breath of the swamp animals: "Vitandam paludum propinquitatem, eo quod, dum auræ matutinæ cum sole oriente ad ædificium preveniunt, adjunguntur his ortæ nebulae, ac spiritus bestiarum palustrium venenatos cum nebula mixtos in habitatorum corpora flatus spargunt, et locum pestilentem efficiunt."

For seventeen centuries these views regarding the development of swamp fever had rested until Lancisi (1718) in his celebrated book: "De noxiis paludum effluviis" again brought them forward and elaborated them most effectually; in the meantime the microscope had been discovered and by its aid animalculæ were discovered in decaying material. Lancisi in the first place determined that swamps represented a favorable breeding place of insects: "paludes copiosum esse insectorum seminarium"; gnats were particularly troublesome: "potissimum molestum illud chrysalidum genus, quod venit sub culicum nomine, et Virgilius humoris alumnum, Politianus vero fertilibus, ut Venus, ea aquis natum appellat." To prove the enormous multiplication of gnats in swamps he quotes the historical facts reported by Pausanias, according to which, the inhabitants of Myons, after an extensive swamp had arisen in the neighborhood of the city owing to the silting of the mouth of the river Meander (Mendere), were compelled to immigrate to Miletus, because of the enormous numbers of gnats. By means of the proboscis and prongs of these insects and also of smaller insects which could not be recognized with the naked eye, the poisonous substances arising from the putrefying organic material under the influence of the heat of the sun, could be introduced into the bodies of the inhabitants. He also does not consider it impossible that even small living bodies might be introduced into the wounds by the insects which caused them. As to whether smallest animalculæ also enter blood in fevers as well as in pests he does not consider himself competent to give an opinion, because he has not investigated this subject. "Porro vatem, non philosophum agerem, si experimentis destitutus affirmare auderem, in castrensibus ejusmodi febris vermes ad sanguinea quoque vasa penetrare, atque ascendere." It required almost two centuries before the assumption, as it forced itself upon the simple observer as the most natural explanation for the origin of paludine fields, namely that they were produced by gnats, had been scientifically proven as an irrefutable fact.

The view that gnats or mosquitoes participated in the causation of the disease did not find believers, especially because the extremely bad condition of the air, the "malaria," of swampy regions, the mephitic vapors which arose during the hot season from the swamps which were filled with decaying and disintegrating organic material—the miasmata of the marshes—in the first place occupied the attention. It was a fact that a person who, especially toward evening upon the setting of the sun or during the night, exposed himself to the visible or noticeable dense, moist vapors which arose from the

swamps and hovered over them was attacked by malaria, the frequently peculiar odor of sulphuretted hydrogen of the evaporations served to strengthen the belief in the noxious effects of the same upon man. Therefore, a great deal of attention was paid to these noxious exhalations in order to discover the cause of their harmfulness.

Monfalcon, in 1825, reports exhaustively on these conditions, in his work on swamps and diseases caused by the exhalations of swamps, which was awarded a prize by the Academy of Lyons. The iatrochemists considered the sulphur and salt vapors of these exhalations as the harmful agents. Ramazzini believed that the particles contained in the paludine air caused the blood to coagulate, thus producing putrefaction of the animal humors. Friedrich Hoffmann thought that the evaporations of swamps caused the air to become dense, rendering it unfit for respiration, disturbed the blood and all the secretions and excretions of the body, thus being instrumental in accumulating the juices in the organism and creating a great tendency to putrefaction. Numerous investigators busied themselves with researches on swamp air. According to Baumes, the air in marshy regions consists of hydrogen, nitrogen, carbonic acid gas and ammoniacal gas, and is a product of the putrefaction of organic substances; it contains aroma foetidum, a high degree of humidity, and, finally, non-visible substances which combust spontaneously. Upon this deficient analysis he has based the following one-sided theory demonstrated by experience (says Monfalcon), of diseases of swampy regions: "If hydrogen predominates, there arise erysipelas, suffocation, sudden death; the prevalence of nitrogen causes headache, gastric disturbance, syncope and coma resembling death; the predominance of ammoniacal gas produces malignant putrid fever and petechial fever, dysentery, bloody abscesses, disgusting, gangrenous ulcers; the combination of all these substances produces intermittent fever."

According to Balme, the fevers are caused by a substance which he called *septon* or azote saturated with oxygen. Tertoris maintained that the exhalations of the swamps originate changes in the air which are conducive to a combination of various kinds of particles, the action of which upon the animal economy would produce more or less injurious changes. Gattoni, Dioeze and others examined comparatively and chemically, the air over swamps and upon unobstructed hills—the analyses of the most healthy and of the most unhealthy airs furnished the same results. Moscati suspended, three feet from the ground, in a rice field, glass balls filled with ice, the surfaces of which, on the following day, were covered with condensed vapors. These he enclosed in a bottle and subsequently the vessel showed a flocculent mucous substance which spread a fetid odor. The same experiment was made in a hospital in Milan between the beds of patients; the accumulated condensed vapor manifested the same properties. Rigaud de Lisle performed a similar experiment, he placed a frame of light, white wood upon four feet and upon this frame he laid three or four large panes of glass in a rhomboid form the ends of which covered each other like tiles. The paludal vapors condensed upon this and then emptied into a large bottle. In this manner two bottles of fluid were collected and sent for examination to Vauquelin, who gave the following explanation in regard to them: "The material is bright and colorless and upon stirring shows flakes; it emits a feeble sulphurous odor

resembling calcified albumin; silver nitrate, lead and mercury indicate the presence of a nitrate salt and an alkali, the precipitate is yellowish, weighs at most from two to three grams, has a saline base, turns black over a flame, effervesces slightly with acids, and precipitates silver nitrate as a yellowish mass. The fluid contains, besides, an organic substance and ammonium, sodium chlorid, and probably also sodium carbonate."

These chemical investigations as a final result absolutely failed to shed light upon the nature of swampy exhalations and upon the manner and method in which their noxious constituents acted upon the organism. There remained but the assumption that the air of swamps contained an unknown principle which could not be recognized by the usual methods of examination.

Many physicians denied absolutely the existence of a swamp miasm, because if it were present it ought to act in a specific manner and should constantly produce one and the same disease, whereas the maladies which arise in various marsh regions in reality differ from one another—an objection which was not, however, considered tenable by others, because variations in the manifestations of the disease might be brought about by varying climatic conditions, by different properties of the soil, such as a predominant amount of organic or vegetable material in the same, iron sulphate or magnesium sulphate, salt water or fresh water and, finally, by the peculiarities of the inhabitants of the swamps which may vary considerably. In other respects these affections always betrayed themselves in the same manner, in so far as they nearly always presented an intermittent type and implicated the same organs.

A uniform cause for the intermittent swamp fevers was suggested by the fact that they were all curable by the same remedy, cinchona bark. Upon the introduction of cinchona bark into Europe its effects were everywhere studied, all opinions were unanimous that the bark removed the cause of the fever. The cause was quite generally considered to be a "*fermentum febrile*" or a "*miasma epidemicum*," and discussions arose as to whether the latter was located in the fluid or in the solid parts of the body, or in both. But most generally acknowledged was the view which was first promulgated by Mundius, subsequently by Borellus, Morton, Cole, Swieten, and others, that the ferment had its seat in the nervous system, the irritation of which caused the attacks of fever.

When, by the discovery of the vegetable nature of yeast and of the fungus of the muscardins of the silk worms, and also by the investigations of Pasteur regarding the specific generators of the various fermentations, of the putrefaction and of the diseases of wines, the idea of the *contagium animatum* had been resurrected, the study of the malarial diseases regarding their eventual parasitic character was also taken up. The first to undertake investigations from this point of view was Mitchell. In an article published in 1849, he ascribed the origin of malarial and of epidemic fevers in general to a cryptogenetic cause. He was followed by Barnes and Gigot, Eklund, Lemaire, the discoverer of the antiseptic properties of carbolic acid, Massy, Wiener, Baxa, Holden, and, above all, Salisbury, whose investigations created the greatest sensation in the entire medical world. He found numbers of oblong, nucleated cells in the sputum of patients suffering from intermittent and re-

mittent fevers. These same cells he discovered also upon the evaporations of the soil of malarial regions, precipitated, according to the method of Lemaire, upon panes of glass, along the shores of the Ohio and Mississippi. The spores, according to his opinion, belonging to a species of algæ growing in the swamps—*palmella*—entered the atmosphere by means of the ascending air current and were then introduced into the respiratory and digestive apparatus of man. To prove the correctness of this view that *palmellæ* were the generators of malaria, he performed an apparently demonstrative experiment. He placed the earth of a malarial soil which was abundantly permeated with *palmellæ* into several boxes, removed the latter into an elevated region which was entirely free from malaria and placed them upon the window-sill of a bedroom occupied by two young men, situated in the second story of a house. The windows, in keeping with his orders, were to remain open continually, day and night. Six days later both occupants of the room complained of malaise, and twelve days later one of them, and fourteen days later the other, had a typical attack of fever. The latter assumed the type of a tertian fever and was cured by quinin. Four members of the family who slept in the lower story of the house were not attacked. A similar experiment which was performed in the same manner in a neighboring building, in a room occupied by a man and two boys, led to the same result, in that both boys became affected by intermittent fever, one after ten days, the other after thirteen days.

The statements of Salisbury very soon found numerous confirmations. Von der Corput reported that he was attacked by malaria when he had cultivated algæ and other swamp plants in his bedroom. Hannon made similar reports. Balestra found a species of algæ which multiplied especially rapidly, and the spores of which could be demonstrated in the atmosphere. Selmi arrived at the same results after the examination of the fogs that arise from the marshes of Mantua. Schurtz reported that in Zwickau, where the disease is extremely rare, an individual who raised *oscillariæ* in his bedroom was attacked by malaria; Schurtz believed that these plants are in a genetic relation to *palmella*. Bartlet found the *palmellæ* to be enormously distributed in a malarial region of the Mississippi. The regions of propagation of this algæ and of malaria were completely congruent. It is quite conceivable, therefore, that the theory of Salisbury of the malaria *palmella* found many adherents. However, the confidence in the works of Salisbury was severely shaken when many of his findings of spores of algæ turned out to be, in the eyes of the experts, simple contaminations of his preparations; and his theory came to an end when Wood and Leydig swallowed thousands of *palmellæ* without becoming affected by malaria.

The statements of Magnin, who assumed a species of *oscillaria* to be the cause of malaria, were as little credited as those of Lanzi who meant to trace the formation of the malaria poison to a peculiar filling of algæ with black granules which might be identical with the globular bacilli of Cohn or with the bacteridium *brunneum* of Schroetter, which represented the proper infectious principle. In this work we already recognize the influence of the beginning bacteriological era; however, it was but little noted at that time. But general attention was aroused by the experiments which Klebs, one of the pioneers in the realm of bacteriology, jointly with Tommasi-Crudeli, tried

in the Pontine Marshes and in the Roman Campagna. These investigators found in the soil, as well as in the air, of these malarial regions, spore-containing bacilli, the culture of which they accomplished successfully. With these cultures, then, in their opinion, they were able to produce, typical intermittent fevers in rabbits, which, frequently, as do the pernicious forms in man, caused rapid death of the animals. Marked swellings of the spleen and melanemia apparently proved in a most conspicuous manner the identity of these animal affections with the malaria of man. Numerous investigators, especially among the Italians, set about to examine the highly interesting statements of Klebs and Tommasi-Crudeli. And, indeed, Ceci found the "bacillus malariae" in the blood of rabbits into which he had injected swamp water; Marchiafava, Perroncito and Ferraresi found the bacillus in the blood of individuals suffering from malaria; Marchiafava, Ferraresi and Sciammana even obtained it from the blood directly aspirated from the spleen of such patients; in fact, Marchiafava and Ferraresi found numerous bacilli in the blood during the chill at the onset of the attack; but they noted that during the acme of the attack, the bacilli disappeared and only its spores circulated in the blood. Cuboni, finally, succeeded in cultivating the bacillus from the aspirated splenic blood of living individuals and from sections of the spleen of persons who had died of pernicious malaria, whereas his results were negative when experimenting with spleen sections of individuals who succumbed to other affections.

Thus, it appeared that the "malaria bacillus" was positively demonstrated scientifically.

Schiavuzzi, in 1889, confirmed the statements of Klebs and Tommasi-Crudeli. He cultivated, from the air over the marshes near Pola, in Istria, a bacillus with the cultures of which he claimed to have produced intermittent fever in rabbits.

In spite of their apparent absolute demonstrative power, however, all these investigations were received with a great deal of skepticism on the part of the physicians. The bacillus malariae was possessed of nothing whatsoever specific that distinguished it from other ordinary saprophytic bacilli, and the "typical intermittens affections" of rabbits were not acknowledged as such by an objective criticism. It was the merit of Golgi, by experiments of his own with the bacillus cultivated by Schiavuzzi, to have exhibited in a strictly critical manner, the numerous objections which could be raised against the malaria bacillus. The result of his criticism was that the malaria bacillus of Klebs, Tommasi-Crudeli and Schiavuzzi had nothing whatever to do with the origin of malaria. The episode of the "malaria bacillus" in the etiology of malaria is an interesting demonstration of how a preconceived idea, even in science, may so dominate investigators that they lose all self-criticism and blindly construe everything they observe in a sense exclusively favoring their views.

Even long before the malaria bacillus had been finally disposed of by Golgi, the last phase in the investigation of the etiology of malaria had begun. The fervently wished-for solution of the problem was furnished by the microscopical examination of the blood of malaria patients. The French military surgeon, A. Laveran, who was stationed in Algiers, was intent upon knowing

how the characteristic blood pigment arose in the blood of malaria patients. To accomplish this, he began to examine the blood of such patients microscopically. During these examinations he determined that the blood contained leukocytes carrying melanin, but, besides, some peculiar spheric, hyaline, non-nucleated, usually pigmented, bodies, and extremely conspicuous characteristic structures of crescent shape. When he, on November 6, 1880, observed the above named pigmented formations under the microscope, he observed at the border of several of these elements, movable threads of flagella, the extremely lively and varied movements of which caused him at once to be certain that these structures were of an animated nature.

In the same manner did Obermeier, in 1868, discover the delicate spirochæte in the blood of relapsing fever patients. In this case it was also due to the striking movements of the parasitic elements which caused a rotary motion of the blood corpuscles that their discovery was accomplished.

Naturally, it occurred at once to Laveran that these parasitic elements were bound to be the cause of melanemia and, at the same time, of the attacks of malaria. He went to work at once to pursue his discovery in the abundant clinical material at his disposal. He found the remarkable flagella in 92 among 432 malaria patients examined; in 389 he determined spheric bodies consisting of a hyaline colorless substance of varying size, of 1 μ in diameter to the size of a blood corpuscle. They were either free in the blood or adherent, "accolé," to blood corpuscles. He found three or four such structures upon some blood corpuscles. These elements possessed distinct ameboid movements. The smallest were entirely free from pigment or contained only one or two pigment granules, whereas the largest enclosed larger quantities of the same which was arranged in the form of a crescent or irregularly.

The smallest non-pigmented corpuscles he considered to be the "forme primitive, embryonnaire des parasites du paludisme." They derived their nutrition, according to his opinion, from the red blood corpuscles, as these became more pale with the growth of the parasites and finally disappeared entirely, whereas the pigment in the former became more abundant. From the spheric bodies of moderate size he noted, best fifteen to twenty minutes after the blood had been drawn, the flagella, which were 21 to 28 μ long and which frequently showed a slight swelling, to pass out in numbers of one to four. During this phase of the structure it appeared as if he were dealing with parasites with pseudopodia. However, the fact that these structures became detached and independently moved with great rapidity between the red blood corpuscles so that it was not possible to follow them with the microscope, caused him, apart from the varying number of the structures, to discard such an idea. "Il est évident," says Laveran, "que chaque flagellum vit à ce moment d'une vie indépendante." He considers the flagella to be the especial, and at that, the most characteristic form of the parasites. "Les flagellas, quoique assez rares dans le sang périphérique n'en demeurent pas moins les éléments les plus caractéristiques et par suite les plus importants parmi ces différentes formes que prennent les parasites du paludisme."

He also considers the cylindrical, crescent-shaped structures which are slightly pointed toward the ends and which carry pigment in the centre to be

very characteristic "mais il le sont surtout, parceque leurs rapports avec les flagellas ne semblent pas douteux." When observing these crescents he noted under the microscope that they became transformed into ovals, finally passing into rounded, motionless, pigmented bodies which appeared to him to be a "forme cadavérique" of the crescents. He often noted the horns of the crescent connected by a fine line which, according to his opinion, was due to an almost complete corpuscle and which suggested the thought to him that he was dealing with blood corpuscles which were attacked by the "hématozoaires du paludisme." Laveran found but rarely, thus in a case of quartan fever, spheric elements which were distinctly segmented and in which the pigment was accumulated in the centre. He ascribed but slight significance to these structures, the fundamental importance of which, as we shall see, was only recognized by Golgi. Finally, he also found irregular, immotile, hyaline, pigmented structures which he took to be cadaveric forms of the parasites, through the incorporation of which the leukocytes became charged with melanin.

He found the above-described parasites 432 times in the examination of 480 malaria patients. The majority of the negative examinations occurred during the first time of his investigations when he was not yet sufficiently familiar with the conditions under which the observations were to be undertaken, and they concerned patients who were treated by quinin.

The observations of Laveran were soon afterwards fully confirmed by Richard. The very motile flagella, in his opinion, were also absolutely demonstrative of the parasitic nature of the structures found by Laveran. Nevertheless, they were not at once acknowledged by the investigators of malaria. The Italian authors, Marchiafava and Celli, even in 1884 did not consider the structures found by Laveran to be anything else but degenerated blood corpuscles, and the flagella to be products of decay. On the other hand, they now found in their blood examinations of malaria patients, which they made in Rome, small non-pigmented, micrococcus-like formations which were often situated in the red blood corpuscles and which became particularly prominent in dry preparations stained with methylene blue. In these corpuscles they observed distinct ameboid movements and, therefore, declared them to be the true parasites of malaria. They designated them by the name plasmodium or hemoplasmodium malariae. Their claim to have found the true generators of the disease has been most decidedly, and unquestionably justly, refuted by Laveran, for he had already described these small structures. But, nevertheless, the observations of Marchiafava and Celli were not without significance, for progress in the recognition of the parasitology of malarial diseases, for they formed the starting point of a discovery of an especially important group of the same.

Many objections were raised against the view that the structures found in the blood corpuscles were parasites at all. The investigations of Mosso regarding the changes which the blood of dogs, introduced into the abdominal cavity of chickens, undergoes in the latter, have played a special rôle in this question. This blood was said to present pictures fully identical to the blood of malaria patients. The erroneousness of this view was proven by numerous investigators by a great number of facts. Nevertheless, the very remote

resemblance of pathologically altered blood corpuscles to malarial parasites has created much confusion in a great many minds up to the most recent times.

The most important, fundamental advance in the recognition of malaria was due to the excellent investigations of Golgi. The latter had the good fortune of being in a position to examine a large number of cases of pure quartan fever in Pavia. Owing to continuous, careful observations of the parasites during the entire course of the fever, he recognized that there existed a very distinct relation between the parasite and the type of the fever, that the intermission, which was so very problematical until then, was due to the developmental cycle of the parasite, that the onset of each attack of fever corresponds to the maturing of a new generation of parasites. He discovered that the development of the parasites takes place in that at first small non-pigmented plasmodia enter the blood corpuscles, that they grow within the latter, absorbing the hemoglobin and transforming it into melanin, that the adult, pigmented parasites after three days assume a neat rosette or daisy-form in which the pigment is accumulated in the centre and, finally, disintegrates into six to ten segments which now as young parasites again enter new blood corpuscles and again begin the same cycle of development lasting three days.

In the following year, Golgi began investigating tertian fever. He succeeded in also discovering an analogous cycle of development of the parasites which corresponds to the course of the fever. Only the parasites appeared to be slightly different from those in the quartan fevers, both as to size and especially as to the formation of the dividing structures. The number of segments produced by an adult tertian parasite was larger, it amounted to about 18 to 20 and the spheres resulting from the division were not arranged so neatly and regularly around the centre as in the quartan forms, but they formed rather irregular clusters.

Golgi concluded from these observations that the various types of fever were due to various species and varieties of parasites.

He succeeded in a number of cases of the quotidian type of fever in determining that they were caused either by three generations of the quartan parasite, or by two generations of the tertian parasite.

Golgi in his quartan or tertian fever never found the crescents which were described by Laveran. Necessarily, therefore, they belonged to the developmental cycle of another species which was as yet not recognized.

The parasitic findings of Laveran, Marchiafava, Celli and Golgi were confirmed during the following years, by numerous investigators in other countries, thus by Councilman, Osler, Sacharoff, Dock, Soulié, Plehn, von Jaksch, Mannaberg, Rosin, and others, so that the parasitic nature of malarial fevers could be considered as generally acknowledged. However, the statements of Golgi regarding the various species of parasites and their typical development corresponding to the course of the fever, met with a great deal of contradiction. Laveran recognized only one parasite, the cycle of development of which included all forms. The numerous Italian investigators who were very solicitous regarding the study of malaria in their own country, which is so severely visited by the disease, were almost of one accord, that the quartan and tertian fevers were due to a separate well-characterized parasite, but they

were of a very different opinion regarding a great number of fevers which, owing to their peculiar epidemiological conduct, were comprised under the name of estivo-autumnal fevers, and in which these investigators had observed the small non-pigmented ameboid forms which they designated by the name of plasmodium.

This group of fevers was clinically distinguished from the others in that the fever type in them was not as regular as in the quartan and tertian types, that a tertian as well as a quotidian type occurred with brief apyrexia and with an inclination to subcontinuous or continuous, more or less irregular, fever, and that they very often assumed a pernicious character. All observers have determined, in individuals suffering from these fevers, besides the small plasmodiæ, also the crescent forms. Marchiafava and Bignami were of the opinion that the irregularity of the fever in this group was only an apparent one, and that it rather contained two fundamental types, the tertian type and the quotidian type, to which two varieties of parasites corresponded with a cycle of development of one, perhaps of two, days, that, therefore, they were in accord with the doctrine of Golgi.

According to their theory, the quotidian parasite is a small non-pigmented ameba which grows but little and contains no, or only very little, pigment. Sporulation takes place even while the parasite is present in the blood corpuscles; however, not in the peripheral blood but in the internal organs and for this reason only very rarely were divided forms found at the beginning of the attack. The parasite alters the blood corpuscles in a peculiar manner. They are decreased in size, shrunken and of a dark color, resembling brass, for which reason they are designated as "*brass-colored blood corpuscles*."

In the tertian type of estivo-autumnal fever the parasite is similar to that of the quotidian type, but its development takes place within three days. At the acme of the fever the smallest ring-like or disk-like ameba are found, without pigment. These show, toward the end of the attack, which lasts twenty-four to forty hours, a little pigment. They grow slowly during the period of apyrexia until they have attained one-fourth or one-half the size of blood corpuscles. With the onset of an increase in the fever, which usually takes place without chill, the parasites disappear to sporulate in the internal organs. They may then even be entirely absent in the peripheral blood. Only rarely and in very severe cases are sporulating parasites found also in the peripheral blood, the pigment of which has collected in the centre or slightly excentrically.

Crescent forms occur in both types of fever; they are distinguished by a remarkable resistance to quinin and are probably the cause of the relapses.

Bastianielli and Bignami have investigated the development of the crescents and ameba. By puncture, from the spleen they obtained small, oval or spindle-shaped particles enclosed in blood corpuscles, which they observed developing into large crescents or round bodies. They believed, as they had never noted sporulation of the crescents, that they represented sterile forms of this fever group.

Canalis conducted very careful observations of the parasites of estivo-autumnal fevers. By reason of his investigations he came to the conclusion that they were not the result of true forms of parasites but only due to a

single one which he called "a variety of the semilunar forms." According to his researches, which he carried on in forty patients in Rome, the parasite, which in its youngest form manifested itself as very small (one-sixth the size of a blood corpuscle), non-pigmented, round ameba, has a very rapid course of development in fresh cases during the first attacks, whereas, later on, it is always slow in developing and corresponds to the phase of the characteristic crescents. The terminal phase in both types is the sporulation form. The first phase of the rapid cycle of development runs its course exactly as we have seen above. The sporulation forms are similar to those of tertian fevers, but poor in pigment, the number of spores amounts to 6 to 10.

In the second cycle, that of the crescents, Canalis distinguishes four phases. The first phase is equal to that of the first phase of the first cycle, therefore that of sporulation. Then, however, the parasite assumes an elongated oval form, whereas the pigment accumulates in the centre and then commences to curve and thus it forms a crescent. After the blood corpuscle has been destroyed, the parasite is liberated. The crescents are followed in the blood by the oval and round bodies which result from the crescents, or again may develop directly.

The round bodies segment and sporulate. The sporulation forms contain 8 to 10 oval bodies which are arranged around a small speck of pigment or wreath. As a product of sporulation, free round corpuscles are noted, being deposited around small masses of pigment and, simultaneously with the renewed attacks of fever, again the small ameboid initial forms. In the second cycle, Canalis also found the flagella of Laveran, which are said to appear after the crescents simultaneously with the round structures.

Several generations of parasites are usually found at the same time in the blood in both cycles.

Regarding the duration of the second, slow, cycle, it varies in different cases, according to Canalis. The ameboid forms require no less than three to four days to pass into crescents. After the latter have appeared, round structures may occur even on the following day. These, however, may persist for a varying period of time before they commence to sporulate.

Antolisei and Angelini arrived at results which were similar to those of Canalis; they also believed that only a single variety, which they named hematozoön falciforme, produced these fevers, and claimed for the same a double cycle of development, a rapid one in which the crescent did not occur until after several preceding attacks, and a slow one in which the latter developed from the very beginning.

The *irregular fevers with long intervals* now became subject to a special critical examination. According to Golgi, they were said to be produced by the parasites of the crescent form, whereas, according to Bignami, they did not form a separate fever group but should be considered only as relapses of different forms of fever, especially, of the estivo-autumnal form.

The investigators who studied malarial diseases in other countries were not able to give more minute information regarding the nature of the crescent forms which were frequently found there.

The capability of the crescents to pass into sporulation forms, contended by Canalis, did not meet with general approval. Thus, for instance, Pes was

never able to observe any sporulation in crescents, although he saw them circulate in the blood for months. He only observed that their number decreased on the approach of the attacks, or that they even disappeared entirely. Grassi and Feletti observed crescents with two nuclei, also with constrictions, so that they regarded these structures as preliminary stages of development. Similar observations were made by Manneberg who was able even to note the total sporulation. Ziemann also found a transverse sporulation of the crescents but he was doubtful whether in these cases it was a question of propagation. Janczó also left this question undecided. All of these observations do not conform to those of Canalis. Only one observer, Lewkowicz, has seen analogous conditions. He writes: "I have observed the transition of an encysted oval-form of a row of crescents into spheres with subsequent excapsulation and sporulation directly under the microscope in the thermostat in two specimens. I also obtained by puncture, from the spleen, sporulation bodies of the crescents, many of which contained thirty spores."

Nevertheless, the capability of the crescents to multiply by segmentation has not been acknowledged. Not until recent times, after the solution of the malaria problem had been successfully accomplished to its fullest extent, has this mode of propagation been observed by G. Maurer as being actually present. He enunciates the view that the crescents, apart from their great importance, as we shall see, for the future existence of their kind outside of the human body, possess another property, namely that of permanent forms, i. e., forms which the parasite assumes to escape certain deleterious effects and which it retains up to a period in which an opportunity for further development by sporulation becomes more favorable. Maurer writes: "How long the crescent is able to live as such in the blood, whether it is bound to perish after a certain period of time unless it has sporulated previously, or whether all crescents make this attempt before the end of their life, this and other questions are still unanswered." The pathogenic segmentation of the crescents would furnish a fully satisfactory explanation of the relapses and especially those arising after long intervals.

Before describing the further development of the malarial parasites, it appears necessary to discuss the question more thoroughly: How does malaria act in its main area of distribution in the tropics? Is tropical malaria different from that variety which occurs in the temperate zones? Are they both due to the same parasite?

F. Plehn who, during a journey to India, had an opportunity of studying tropical malaria was not able to find differences in the blood parasite observed by himself and by others, neither in the morphologic nor in their staining properties from the malarial parasites which were observed in Germany, Italy nor in tropical regions; he was, however, not able to determine the type of the fever from the blood examination.

E. Grawitz found in the blood of the members of the East African military garrison, among the soldiers that suffered from irregular fevers, ameba and crescents.

Bein observed ameba and crescents in a man from Brazil, who suffered from quotidian fever.

Dock favored the identity of tropical and domestic malaria.

Thayer and Hewetson in an excellent article reported 616 cases of malaria in Baltimore; they were able to determine the exact variety of the parasite in 542 cases. They only found three varieties, the tertian, quartan, and estivo-autumnal parasites, the cycle of development of the latter being from twenty-four to forty-eight hours. They found:

The tertian parasite: single infection.....	150	times
double "	188	"
The quartan parasite: single infection.....	2	"
double "	0	"
triple "	3	"
The estivo-autumnal parasite: single infection.....	188	"
conjointly with tertian parasites.....	11	"

In the cases in which the estivo-autumnal parasite was found, the fever was sometimes continuous, as different series of parasites were present in the blood or because segmentation occurred continuously.

Van der Scheer, who studied malaria in Java, by reason of these studies, arrived at the conclusion, that at least two species could be assumed, one a large variety which produces the tertian and quartan fevers with their varieties, and a small one, which causes the malignant quotidian, tertian, remittent and pernicious fevers.

F. Plehn, who primarily was in favor of the identity of the temperate and tropical fevers, changed his views, after having an opportunity of gathering observations in Kamerun regarding black-water fever. He found in the blood of patients, a very small ameba, staining with great difficulty, which was different from all other malaria parasites known up to that time, which formed no pigment but, nevertheless, was able to dissolve hemoglobin in the blood serum. This parasite also differed from all others in that it was not influenced by quinin.

Ziemann, who also had an opportunity of studying malaria in Kamerun, besides this, however, in patients from Mossamedes, Portuguese Angola, Mohammerah on the Persian Gulf, from Trinidad and from Lehe, arrived at the opinion that there were two varieties of parasites, a large variety which gave rise to domestic tertian fever, and a small, usually ring-form, which caused tropical fever. In the small parasite of tropical fever, he considered a two-fold development possible. Either the parasites sporulated or they were changed into large endoglobular forms with actively motile pigment, to spheres, flagella or crescents. He particularly emphasizes that malaria which is due to the small ring-formed parasites might appear with a genuine quartan type.

Marchoux found parasites in Senegal, which appeared to be identical with the estivo-autumnal parasites of the Italians and which completed their course of development in twenty-four hours, however, producing less pigment than the former. Production of pigment may be entirely absent. He recognizes but one parasite, agreeing with Laveran, and believes that the parasite of the quotidian fevers in giving rise to the tertian or quartan type depends upon the resistance of the individual.

Däubler did not consider the question as decided as to whether the tropical parasites discovered so far, the East Indian, those from Kamerun and the Italian small parasites were all identical, as they differed in some details, but he believed that it was not a question of different species.

Laveran, finally, upon the basis of geographical study of malaria, arrived at the conclusion that everywhere upon the entire earth the identical clinical form of malaria appeared, that nowhere did one or the other form exist exclusively, that the same polymorphic parasite was found everywhere.

In a review of these statements, it follows that unanimity regarding the different forms of malaria and their parasites occurring in the most varied countries by no means existed.

R. Koch in commencing his studies of malaria accordingly considered it one of his first duties to make a comparative examination of patients in as many localities as possible, especially in tropical regions, and to obtain evidence regarding the variety of fever that was present and the parasite giving rise to it.

The result of these thorough investigations carried out in Italy, in East Africa, in Batavia and in New Guinea, was: There are three fundamental types of fever, the tertian, the quartan, and the tropical tertian, the latter designated by Koch briefly as "tropical fever," which is identical with the estivo-autumnal fever of the Italians. Three sharply defined characteristic varieties of parasites correspond to these three fever varieties, the large parasite differing in the duration of its cycle of development, so that a tertian and a quartan parasite may be recognized and the small form appear as rings, the parasite of the tropical fever, the cycle of development being tertian and the crescent shape alone being peculiar to this parasite.

This important decision, which simplifies the malaria problem exceedingly, and which up to that time was in great confusion, was arrived at by Koch by the exact clinical observation of recent cases that were uninfluenced by treatment, on the one hand, and by continuous laborious blood examinations of each individual case with the aid of cover-glass preparations in which the details of the different parasitic forms could be discovered with much greater ease, distinctness and certainty than in fresh unstained blood preparations, on the other hand. This determination of Koch, as we shall see later on, is especially important in reference to prophylaxis and treatment.

However, with the discovery of the developmental cycle of the malaria parasite in the blood of the patient by Golgi, and with the demonstration of the different kinds of parasites, the malaria problem was by no means solved as yet.

A great number of the parasite forms observed in the different varieties of fever, the large, free, round and oval bodies in the tertian and quartan fevers, and the crescents in the estivo-autumnal fevers, did not conform to Golgi's cycle of development.

It was especially that form of the malarial parasite which had been the starting point of all investigations and which was regarded by Laveran as the highest stage of development of the parasite—the flagella form—with which nothing could be done. The flagella forms were occasionally found in all varieties of malaria, and Laveran founded his doctrine of the uniformity

of the malaria parasite upon this fact. The appearance of the flagella was quite generally considered as a phenomenon of decay of the parasite, quite in contrast to Laveran.

However, further investigations have shown that Laveran was right in his estimations of the flagella forms. Not until the significance of these remarkable and characteristic forms was recognized did the problem of the propagation of malaria find its final solution.

Three factors have been instrumental in bringing about this solution, 1st, the recognition of the final structure of the parasite, especially of the part most essential to its propagation, the nucleus, 2d, comparative embryonical studies of the malarial parasites and of the lower animal organisms closely related to them, and 3d, the pursuit of the so-called mosquito theory, the idea of the transmission of the disease by means of mosquitoes.

The first ones who endeavored to obtain a knowledge regarding the finer structure of the plasmodia, with the aid of special histological methods, were Celli and Guarnieri. They distinguished an easily stainable ectoplasm and an endoplasm which stained but weakly or not at all. Sometimes they observed in the pigmented forms in the endoplasm a sharply defined body which contained two intensely stained bodies. They were inclined to consider these bodies as genuine nuclei.

Feletti and Grassi, then, by means of special methods, determined the presence of a vesicular nucleus, which was supplied with a nucleolus, in all forms of the parasites.

They observed, in the growth and in the segmentation, an enlargement of the nucleolus and then a division of the same into small nucleoli, each of which was said to be surrounded by some nuclear fluid and by an extremely delicate membrane. Each nucleus was said later to become surrounded with some protoplasm. The pigment and probably the peripheral part of the plasma were reported to accumulate in the residual sphere remaining after segmentation had taken place. They called these new-formed bodies gymno-spores.

Mannaberg arrived at similar results with the application of a new method of fixation and tinction (fixation with picrin-acetic acid and staining with hemotoxylin).

He distinguished the cytoplasm from the vesicular nucleus with nucleolus. In the cytoplasm he recognized two zones, one rich in pigment, external one, which stained well and which he called ectoplasm, and an internal one, poor in pigment, staining weakly—the endoplasm which surrounds the nucleus that is always situated externally to the plasma. According to his observations, the nucleolus increases in size, then diminishes in its staining properties and now shows in its interior deep-dark, punctiform deposits. Subsequently a vacuole occurs in the nucleolus, the latter becomes faveolate and then disappears. The nucleus then becomes rich in chromatin which, as Mannaberg believed, flowed in from the cytoplasm through the injured nuclear membrane. Thereupon the nucleus stains, so that it is distinguished from the cytoplasm only by the absence of pigment. In the half of the nucleus there occur, mostly sharply defined granules which stain darker and which develop into the nucleoli of the new spores. A little later there is a differentiation of the

substance surrounding the nucleoli into a peripheral, stained one (plasma) and into a central, unstained one (nucleus). The formation of the spores is terminated with the occurrence of this differentiation. The process of sporulation, therefore, takes place by a mitosis.

These investigations opened up a road to the comprehension of the growth and method of propagation of the parasite, and they permanently removed all doubts regarding the organized nature of the plasmodia.

However, even these discoveries did not give any information in regard to the nature of the ovals, spheres and flagella.

New light was shed upon the finer structure and the nature of the constituents of the parasites, most essential to the development of the same, by the discovery of a new method of examination. This was found in 1891 by Romanowsky and reported in his fundamental work: *On the Question of the Parasitology and Therapy of Malaria*. The method, with which we shall concern ourselves more minutely later on, is as follows: Malarial blood which is smeared upon cover-glasses is fixed, after Ehrlich, by heating for thirty minutes to 105° C.–110° C. and then stained in a watch glass for one-half to two hours with a mixture of one part concentrated watery solution of methylene blue with two parts of 1 per cent. watery solution of eosin. The malarial parasites then appeared in their principal mass stained blue in the pink colored blood corpuscles. But within the parasites there is always visible a round or oval portion which contains structures of a carmin-violet color and of the most varied forms, which Romanowsky considered to be the chromatin portion of the nucleus of the parasite. Romanowsky has carefully studied a number of malaria cases with this new method, and he recognized that the chromative substance found with his method was of determining significance in the development of the parasite. The growth and, later, the segmentation of the parasites goes hand in hand with characteristic changes and, finally, with a segmentation of this substance, so that each young parasite resulting from this segmentation is supplied with a bright red chromatin granule surrounded by some blue cell substance. We shall later on enter more closely upon the important findings which were established by Romanowsky in the chromatin substance in the parasites after treatment with quinin and which have elucidated the nature of the action of quinin upon the parasites.

Sacharoff has studied, by means of Romanowsky's eosin methylene blue method, which, besides, soon after Romanowsky's publication was also reported by Malachowsky, with a slight modification (Malachowsky advised taking borax methylene blue instead of the watery solution), not the flagella forms of the malaria parasites of man, but the flagella forms which had been found by Danielewsky as a special variety of blood parasites, as "malaria parasites" in various birds and which were described as a special variety of parasites, as "polimitus avium." He discovered in an indisputable manner, from the preparations stained according to Romanowsky, that the flagella arising in these parasites consist of chromatin substance and originate from the chromatin-stained nuclear substance of the same, which divides into some small threads and exudes from the parasite. The separation of the chromosomes in the parasite, which begins shortly after the withdrawal of the blood, is caused, in his opinion, by the cooling of the blood. He then arrives at the following con-

clusion: "As I have demonstrated the identity of the flagella of the malarial parasites with the chromosomes in the most convincing manner, the capability of the chromosomes to execute active movements is irrefutably demonstrated thereby. We also do not doubt that many physiological and pathological processes will be accounted for by the capability of the chromatin to execute independent movements and in this manner to leave the nucleus and the cell itself." The thought, however, that these chromatin fibres which originate in the chromatin, the substance most essential to the life and the further development of the cells, and which become freely movable, might be of importance for the further development of the parasites, did not occur to him.

Instead, like the majority of all investigators, he considered the flagella producing parasites, for decaying forms, "*formes mourantes*."

Their correct explanation was brought about only by the second factor mentioned above, the comparative embryological study of the malarial parasites and of the lower animal forms related to them, of the blood and cell parasites found in the course of time by the most various investigators in numerous higher and lower animals.

We shall, therefore, briefly consider the position assigned to the malarial parasites in the system.

Laveran designated the parasite discovered by him by the name *hematozoon malariae*, without classifying it in any manner. Marchiafava and Celli called it *plasmodium*, and in one of their first articles already compared it with blood parasites of frogs, the *paramaecioides costatum* Grassi and the *trypanosoma sanguinis* of Gruby, in that they designated the movements of the undulating border of the former and of the flagella of the second as being very analogous to the movements of the bodies of the blood of malaria.

Metschnikoff, who had observed in the cerebral capillaries in the interior of the red blood corpuscles the daisy-like forms described by Golgi and their decomposition into daughter individuals, placed the malaria parasites in relationship with coccidia and proposed to designate them by the name *hematophyllum malariae*. He stated that the malaria parasites, of all coccidia described thus far, bear the greatest resemblance to *klossia soror* described by Aimé Schneider, which also multiplies by the decomposition of the mother cells into daughter spheres.

Celli and Guarnieri who, with Councilman, took the crescents for spores, owing to this sporulation classified the *plasmodium malariae* among the *gregarinae*, and in the order of coccidia.

Feletti and Grassi divided the malaria parasites into two genders, *hemameba* and *laverania*. *Hemameba præcox* was said to be the parasite of quotidian fever, *hemameba vivax* that of quartan fever; *laverania*, distinguished by crescent forms was said to cause the irregular fevers. They classified the parasite, owing to the distinct, large vesicular nucleus which they had found, among the rhizopods, and especially among the *amœbiformes*, as these are also distinguished by such a nucleus. The plasmodia they called *amœbula*, or *ameba*, and the products of their segmentation, *gymnospores*.

Antolisei, who wanted the term *plasmodium* replaced by the name *ameba*, classified them as *proteomixi*, among the *gymnomixi*.

Celli and Sanfelice proposed to embrace all intraglobular parasites of the

vertebrate animals in one class of the sporozoa under the name hemosporidia.

Kruse arranged the blood corpuscle parasites known until then in one family, hemogregarinidæ, with three species: hemogregarina, hemoproteus and plasmodium, into the order monocystidea Bütschli of the subclass gregarinidæ of the class sporozoa. It would lead us too far into zoological details if we meant to discuss minutely all the change of view regarding the position of the malaria parasites in the system. The most essential part of the numerous investigations of the subject is the acknowledgment of their close relationship to certain other lower animal forms, as, for instance, the coccidia. Each progress in the recognition of the propagation of these animal forms occurring in numerous cold blooded and warm blooded animals thus at the same time gained a special interest for the malaria parasite.

Of conspicuous importance, therefore, was the discovery of R. Pfeiffer that in the known coccidium of the rabbit two cycles of development take place side by side, an *exogenous* and an *endogenous* one.

The so-called exogenous circle was known for a long time. Rabbits affected by coccidiosis discharged with their feces permanent spores, oval capsules, the contents of which divide into a number of so-called sporozites. If these sporocysts enter the intestine of the young rabbit with the food, the coarse cover is loosened, consequently broken, the young forms, the sporozoites, become liberated and now enter the epithelial cells to grow there and to develop, finally, again into permanent spores.

R. Pfeiffer then became convinced that the, sometimes actually enormous, quantities of parasites inhabiting the intestinal epithelia could not possibly be the result only of the ingestion of lasting spores per os. He found, upon closer investigation, that all the sporozoites entering the epithelia did not develop into lasting cysts, but that some of them became transformed into so-called zoospores in which enormous numbers of crescent germs arose which swarmed from the cysts, entered into fresh epithelia and in this manner caused the colossal epithelial infection and the dissemination of the latter. R. Pfeiffer, immediately upon the publication of his discovery of the twofold manner of propagation of the coccidia, expressed his belief that, possibly, also in the malarial parasite, in which until then only the endogenous multiplication by segmentation was known, an exogenous mode of development might be present besides.

Another important discovery was made by Schuberg in coccidia in the intestine of the mouse, and by Simond in the coccidia of the rabbit and of the salamander, namely, that the formation of lasting forms, of the spore cysts, is the product of a sexual copulation of male and female germs.

After the so-called endogenous development which leads to further epithelial infection has persisted for some time, the formation of sexually different parasites takes place, from the sexual copulation of which arise the resistant spore cysts which are necessary for the perpetuation of the species and which are discharged from the body. The male germs develop as actively motile, flagella-like, chromatin free structures in the periphery of a larger globular parasite; they are liberated and enter into other large adult parasites poor in chromatin which have arisen from the segmentation of a parasite.

Fecundation occurs, therefore, of a larger female individual—macrogamete—by a small, thread-like individual—chromatozoit or microgamete—in a very similar manner as the metazoön ova are fecundated by a spermatozoön.

Simond concludes from his investigations that the motile stage in the coccidia furnishes the most rational explanation for the flagella bodies of the Laveran parasites of malaria and for the polymitus form found by Danielewsky in birds.

Simond says: "These structures are in all probability the same stages in the hematozoa, and we must admit the possibility, here as in the coccidia, that sexual copulation is necessary to produce a *forme de résistance*." The miasm of swamp fever must be, as it was declared to be by Metschnikoff and R. Pfeiffer, a resistant form in spore condition, analogous to that of the coccidia.

The postulate of a second, exogenous cycle of development, characterized by an act of copulation, of the malaria parasite, derived by R. Pfeiffer and Simond from the development of the coccidia, was shown to be correct; their conclusions from analogy, however, that, accordingly, also in the malarial parasite a lasting form must develop, intended for the perpetuation of the species, was found to be incorrect.

The next step forward we owe to the observations of an American investigator, MacCallum. Again the blood parasites of birds discovered by Danielewsky, which are so extremely convenient for research work, furnished the material for the observations of Opie and MacCallum, and in particular the halteridium occurring in numerous nesting birds, tree-falcons, crows, pigeons, sparrows, finches, etc., protoplasmic pigment-carrying structures with ameboid movements which dwell in the red blood corpuscles of these bird species, surrounding the nucleus in dumb-bell form—therefore halteridium from halteres, dumb bells. These parasites are quite often present in such quantities that dozens of affected blood corpuscles may be observed in one field of view of the microscope. If blood is taken from a markedly affected bird and observed, after being previously diluted with physiological salt solution or, better still with homogenous blood serum, we note how these structures pass out from the blood corpuscles, become sphere-shaped and, the same as the spherical bodies of the malarial parasites, send forth a number of actively motile flagella which after some time become detached and move away.

Opie, in his studies of this parasite in 1896–97, observed that two forms of parasites existed in the blood of crows examined by him—a hyaline, non-staining one, and a second granulated one which stained dark blue with methylene blue—and that only the hyaline form "might become flagellated."

MacCallum confirmed these observations; he also found that only the hyaline form became flagellated, whereas the granular form, after its removal from the blood corpuscle, remained quietly as a sphere near the nucleus of the blood corpuscle.

MacCallum observed that, after fifteen to twenty minutes, these quietly resting spheres developed motile, spindle-shaped bodies which were identical with the "vermiculus" described by Danielewsky as a special form of parasite.

He then noted, upon careful observation of the two adult forms during their exit from the blood corpuscle, that the flagella of the flagellate form became

detached and immediately rushed upon the granular forms, attempting to enter into the same. Only one of the flagella gained admission and entered, while the pigment in the same became greatly agitated. The flagella, therefore, proved to be fecundating agents, spermatozoa. After fifteen to twenty minutes' rest, the sphere sent forth a conical process which grew and received the pigment until, finally, a spindle-shaped body arose with a slightly pigmented appendix—the vermiculus of Danielewsky. The formation of the vermiculus was always the same. It proved to be very motile and, with its pointed anterior end, it pierced red blood corpuscles, suggesting to MacCallum that the vermiculus might penetrate the walls of the intestinal tract and thus, as a resistant form, reach the external world.

Thus, MacCallum *had, for the first time determined a process of fecundation in a parasite of the group of blood corpuscle parasites, with motile form resulting therefrom, which developed under unfavorable exterior conditions and which was comparable with similar processes in lower animals and plants.*

He then at once expressed the thought that a similar process might be expected in the malarial parasite of man. In fact, he soon afterward succeeded in observing in the human malarial parasite a sexual entrance of a flagella into a non-flagellated spheroid.

This, however, was by no means sufficient to elucidate the development of the human malarial parasite.

The final discovery, and with it the disclosure of the mode of dissemination of malaria, was due, rather, to the scientific experimental pursuit of the so-called mosquito theory, a theory which since ancient times ascribed to the mosquito an essential part of the origin and propagation of malaria.

As we have seen, this old view, although most forcibly emphasized by an investigator of the standing of Lancisi was gradually forgotten. However, it remained in the popular mind in many regions. Especially characteristic in this respect is Koch's report of his travels in German East Africa, in which he states that the Usambira negroes used the word "mbu" synonymously for disease and for mosquitoes, and that with them the belief prevailed that the sting of mosquitoes caused them to become diseased. If savages living in the state of nature arrive at such conclusions in consequence of certain observations, it would be actually incomprehensible if the same thoughts should not suggest themselves to physicians living in malarial regions, individuals who are accustomed to scientific observation. And we actually find that prominent men in different parts of the world had already favored such a view.

In America, according to a review by Nuttall, at first Nott and later King, emphatically defended such a theory. In Germany it was Koch, who by reason of his observations in India assumed a transmission of the disease by the sting of blood-sucking insects, he even expressed this opinion in his lectures.

The origin of malaria was the subject of a symposium in the section for tropical hygiene at the sixty-third meeting of German naturalists and physicians at Bremen in 1890. The disciples of Koch, Fränkel, Gartner, and Löffler, defended the mosquito theory. In 1891 Laveran as well as Flüge expressed themselves in favor of this theory.

The theory was especially made plausible by numerous successful experi-

mental transmissions of parasites contained in the blood of malarial patients and inoculated into healthy individuals.

After Gerhardt had first succeeded in inoculating malaria in this manner, numerous Italian investigators, Marchiafava and Celli, Gualdi and Antolisei, Antolisei and Angelini, Dio, Di Mattei, Bignami and Bastianelli, and others were able with one to two cc. of blood which they injected intravenously and subcutaneously, not only to produce the disease artificially but even the distinct type of the fever which was presented by the patient from whom the blood was taken. The transmissibility of the disease was, therefore, absolutely demonstrated.

Another important fact had in the meantime been discovered by Smith, this was the cause of the so-called Texas fever of cattle. It was found to be a blood parasite living in the red blood corpuscles in a similar manner to the malarial parasite of man, and further, that this parasite is transmitted by insects, ticks, parasites of cattle. Upon closer study of this method of transmission, Smith made the remarkable discovery that the infection was not due directly to ticks that had sucked the blood of the affected animal but that it was caused by their offspring generated from their ova.

Koch who discovered Texas fever in East Africa and who was able to confirm experimentally the observations of Smith, which until then had been received with suspicion, was thereby led to the thought that the transmission of malaria might occur in a similar manner. Nor did he consider it beyond the range of possibility that the malarial parasite might remain alive through several generations in the mosquito. The only method of arriving at an explanation of these conditions was by means of an experiment, which then was immediately undertaken by Koch and pursued by him with his well known vigorous energy.

The study of malaria by an investigator of the character of Koch was followed by such success that all questions regarding the etiology that were doubtful up till then, found a speedy and generally acknowledged solution and, above all, the prophylaxis against the disease was placed upon a new, safe, scientific basis.

His first endeavors were directed, as stated, in familiarizing himself with all the various existing parasites. By examination of stained blood observations and careful clinical observation, he recognized the identity of tropical fever and of the estivo-autumnal fever of the Italians. By the aid of the Romanowsky stain, which he improved, he found that the crescent forms of these fevers and the flagellated forms resulting from them could not be parasites that were destined to destruction because they contained considerable chromatin and because the flagella, originated directly from the chromatin body; further, that in reality they were not flagella but, according to analogy of parasites that were closely related, they were spermatozoa. He did not, for the time being, succeed in advancing further in the pursuit of the development of the parasite but he was able to confirm an important discovery which the Anglo-Indian military surgeon, Ronald Ross, had carried out with an avine blood parasite—the proteosoma.

Manson, in England, had concluded, from the observation of the flagellated forms that can be discovered only after the lapse of fifteen to twenty minutes

after the drop of blood has been drawn, that they represented the first stage of life outside of the human host.

He had recognized, further, the important rôle played by the mosquito in the transmission of filaria and he considered it likely, therefore, that the malarial parasites also passed through their further development in the body of the mosquito. As filaria larvæ which the blood-sucking mosquito introduces into its stomach with the sucked blood develops within the body of the mosquito into a form which, after the death of the mosquito, swims freely in the water and is then capable of infecting man, it was surmised by Manson that the malarial parasite would be capable of further development in the mosquito into infective forms which, after the death of the mosquito, becoming liberated, entered into water or soil and introduced into the human subject were capable of infecting the host. This theory of Manson was accepted by some, whereas it was opposed by others, it being insufficient to explain the origin and propagation of malaria. In Italy it was especially Bignami who expressed himself against this conception of Manson. Bignami had previously attempted to investigate the mosquito theory experimentally, in that he caused human beings to be stung by mosquitoes from malarial territories. He represented the view that the germs of malaria lived in water and infected the larvæ of the mosquito living in this medium. The mosquitoes which result from this infected larvæ were then said to infect healthy human beings by their stings. Manson then caused the English military surgeon, Ronald Ross, to concern himself with the experimental study of this question.

Ross studied the problem in India according to the plan of Manson. He caused mosquitoes to suck from malaria patients the blood, which was rich in crescents, and observed the conduct of the parasites in the stomach contents of the mosquito. Although, he then noted the so-called flagella developing, he did not find any further stages of development. Finally, after two and one-half years of futile experiments, he found, in August, 1897, in two mosquitoes which had speckled wings and belonged to a new species that until then had not been utilized by him and which had been fed upon crescent-containing blood, in the tissue of the stomach a number of round structures containing the typical malaria pigment and which he, therefore, considered to be the long looked-for stage of development external to the human body. He continued his studies in 1898 but then at first he did not concern himself with the malaria parasite of man but with the avine parasite which resembled the former—the proteosoma Labbé—which was observed especially often in sparrows but, besides, also in crows and in weaver-birds. He found that the birds were stung by a “gray” species of mosquitoes, he noted in the stomachs of these mosquitoes the same round pigmented cells which he had observed in the mosquitoes with speckled wings (see Fig. 3).

He then found, further, that these pigment cells rapidly increased in size. Whereas thirty hours after the ingestion of blood, they showed a diameter of only $6\ \mu$ —six days later it amounted to $60\ \mu$.

At the same time they bulged toward the colon of the mosquito, i. e., toward the current of the fluids. In these spherical bodies there developed an enormous number of fine filiform structures which he called “germinal threads” but, besides, a lesser number of peculiar large dark-brown formations

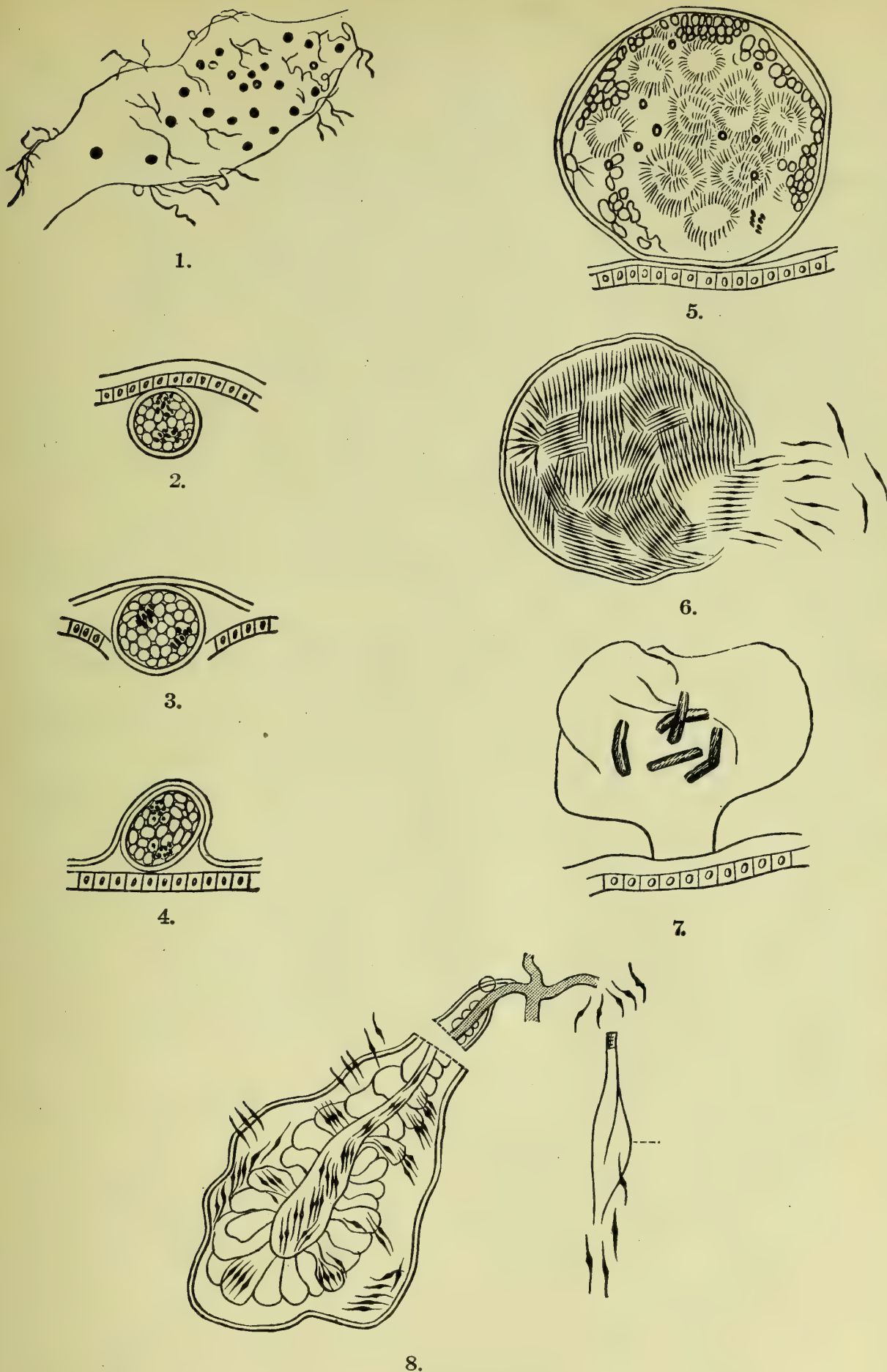


FIG. 3.—DIAGRAMS OF THE DEVELOPMENT OF THE PARASITES IN THE MOSQUITO.
(After Ronald Ross and Fielding Ould.)

1, Stomach with mature zygotes; 2, zygote approaching the internal wall of the stomach; 3, passing through it; 4, detached under the internal membrane of the stomach; 5, mature zygote with blastophores; 6, rupturing zygotes, discharging blasts; 7, black spores; 8, salivary gland of the mosquito with germs (blasts).

of varying curves which he designated "black spores." It was possible to rupture these spheres by slight pressure. This was followed by the discharge of the filiform bodies. According to his account, a similar process occurs in the mosquito, the mature cells rupture and discharge their contents into the colon. The filiform bodies are carried everywhere by the blood current. Ross noted that they accumulated in large masses in the cells of the gland which was situated in the head of the mosquito, in the middle lobe, which he recognized as the poison gland. When the mosquito bites, some secretion of the salivary glands is simultaneously discharged into the small wound and this causes the infection of the individual thus stung. In fact, Ross succeeded in infecting birds that were not attacked by proteosoma parasites with the sting of gray mosquitoes infected with proteosoma. This completed the chain of evidence regarding the development of proteosomæ in the gray mosquito. Now, in reference to the black spores, Manson proposed the hypothesis which was accepted by Ross that these resistant bodies after a certain period of maceration in water were capable of infecting the larvæ of mosquitoes living in the water, thus transmitting the malarial parasite in the mosquito from generation to generation.

Koch, who with Pfeiffer and Kossel in August of the same year studied malaria in Rome, succeeded, corresponding entirely with Ross, in demonstrating the cycle of development of the proteosoma parasite in the species of mosquitoes which he designated as *Culex nemorosus*. He even succeeded in demonstrating in the stomach of the mosquito the formation of vermiculiform structures which were found by MacCallum in the halteridium of birds which arise after fecundation as preliminary stages of coccidia-like spheres; thus the gap was filled that was left open by Ross. Koch also observed the "black spores," the "dark brown structures with the appearance of a knotty, deformed root," but he was very reserved regarding their significance. He illustrated the entire cycle of development of the parasite by excellent photographs. The statements of Ross were also fully confirmed by Daniels.

Thus the unbroken history of development of the entire group of blood parasites, including also the malarial parasites of man, was principally determined.

However, the special method of development in particular of this most important organism was still lacking.

Ross and Koch had learned by investigations that a distinct species of mosquito was necessary to cause the exogenous development of the proteosomæ. Ross, in 1897, had already found coccidia-like pigmented spheres in the gastric region of two mosquitoes with "speckled wings," but he had not defined their species.

It is therefore necessary, by further investigations, to find the species in which the human malarial parasites are capable of development.

Grassi, to whom Koch had explained his ideas regarding the transmission of malaria by mosquitoes, upon his return from East Africa, immediately set to work to make investigations in regard to the blood-sucking mosquitoes occurring in the malarial regions of Italy. He found that three species were always present, preferably two species of *Culex*, *Culex penicillaris* and a new variety, which, owing to their great preponderance at the time of the most

severe malarial infection in Maccarese, appeared to be especially suspicious and which, for this reason, he called *culex malariae* and, finally, a species of *anopheles*—*anopheles claviger* Fabr., a large mosquito with speckled wings which was popularly called *moschino* or *zanzarone*. Upon further investigation he found that this variety of mosquito was not present in malarial regions, for instance, Sicily. All attempts at transmission which were made by Bignami and Grassi with varieties of *culex* in malarial localities of Rome remained unsuccessful. Finally, however, a man became affected by malaria in the experimental room of the hospital after the opening of a vessel containing mosquitoes from Maccarese, among which there were some *anopheles*. Thereupon, Grassi proclaimed the *anopheles claviger* as the true transmitter, “la vera spia,” of malaria, especially as he found it in all malarial regions of Italy, and failed to find it in regions free from malaria, whereas Bignami was inclined to attribute the disease to the *culex penicillaris* or to the *culex malariae*. Koch, who attempted to find in Grosseto the mosquito variety which was appropriate for the transmission of malarial parasite to man, catching the mosquitoes which were present in houses in which recent malarial affections had occurred and then examining their poison glands for the coccidia-like spheres, consequently crescent germs, scarcely ever missed the *culex pipiens*, but, on the other hand, found the *anopheles maculipennis* only eight times in the examination of forty-nine dwellings in which malaria existed, and at that he found only a few specimens and the latter not infected. However, in some localities in which malaria was prevalent he found the *anopheles* in very large numbers, and in seven specimens of these he noted coccidia-like structures, namely crescent germs. Koch writes: “This would point very much to the fact that *anopheles* are primarily the transmitters of the affection.” However, as he also found *culex pipiens* which were affected, he believed it probable that at least two varieties of mosquitoes, *culex pipiens* and *anopheles maculipennis* participated in it, in the above district.

Further investigations have shown that, according to the assumption of Grassi, the *anopheles* must be considered the sole transmitters of malaria.

Grassi, Bignami, and Bastianelli succeeded also in pursuing the cycle of development, at first of the estivo-autumnal, and then also that of the tertian parasites (Bignami and Bastianelli) in the *anopheles*. They also determined certain differences in the development of both parasites. Whereas in the former they almost always observed only 4 flagella, they found 6 to 7 in the male tertian gametes. The young sporozoön in the stomach of the mosquito, which had resulted from the fecundation of the female gametes, was spindle-shaped in the estivo-autumnal parasites, and always round in the tertian parasites; the former was also more refractive to light and richer in pigment. The volume of the nuclei into which the sporozoön divided was larger and their number smaller, the sporozoites resulting from the segmentation were less crowded and were arranged more regularly in the tertian than in the crescent sporozoa and, finally, the number of the granular rounded residual bodies remaining after the segmentation was greater so that the differential diagnosis could be made with certainty, especially in the stage preceding the formation of the sporozoites.

By experiments on human beings, the above-named authors then also

furnished the further proof that the anopheles which harbored mature sporozoites in their salivary glands, by their sting cause the same form of malaria, after a typical incubation stage, with which they had become infected by sucking the blood of a patient. The black spores which Ross and Koch had found in their proteosome experiments, and regarding the significance of which they had been unable to arrive at a final opinion, were also found by the Italian investigators; however, the latter considered them to be retrogressive changes of the sporozoa, an opinion which was also shared by Ruge.

They were able to exclude a transmission of the germs upon the offspring of the infected anopheles, as such anopheles which resulted from the ova of infected females were never able to produce malaria by their stings. The temperature played the principal part in the development of the parasites. The estivo-autumnal parasite did not develop in the anopheles at a temperature of 14° C. to 15° C., but it developed constantly but slowly at 20° C. to 22° C., at 30° C., however, to the formation of sporozoites within seven days. The gametes never developed in the culex; they did so, however, apart from the anopheles claviger, in three other varieties of anopheles, anopheles bifurcates, pseudopictus and superpictus.

The results of investigations of the Italian authors regarding the development of the malarial parasite were confirmed throughout, thus by the English commission under the direction of Ross and, quite recently, by Schüffner in Sumatra, by Schaudinn in Rovigno, and by Tzuzuki in Japan. Authors have generally illustrated their investigations with excellent colored drawings and also by photographs, so that, now, the development of the malarial parasites in the anopheles may be classed among the generally acknowledged and best-investigated chapters of the genesis of malaria. Unobjectionable observations are only lacking as yet in regard to the development of the quartan parasite. Two observations must be particularly emphasized. To preclude all objections to the transmissibility of malaria by anopheles, Manson and Thorburn caused themselves to be bitten, in London, by anopheles which were infected in Italy by a case of tertian fever and then sent to England. Both authors, after an incubation period of fourteen days, in a country entirely free from malaria, became affected by typical tertian fever, showing parasites in the blood.

Schaudinn succeeded in filling the only gap that had remained until then; namely, in following in a vacuole immediately under the microscope, the entrance of the young parasites resulting from the segmentation, of the merozoites, as well as that of the sporozoites from the poison gland of the mosquito, into red blood corpuscles, and the transformation of the same into typical young, endoglobular, pigment-free parasites (see Fig. 4).

Schaudinn also made the important observation that the microgametes of the tertian parasites are able to multiply by segmentation in the body of man (see diagram), that this process takes place shortly before the occurrence of the relapse, that, therefore, the appearance of the relapses of tertian fever are caused by an analogous parthenogenetic process, as was observed by Canalis, Lebkowitz and Maurer in the crescents of tropical fever.

If we briefly recapitulate now what has, until this time, been discovered regarding the development of the malarial parasite of man, at the same time

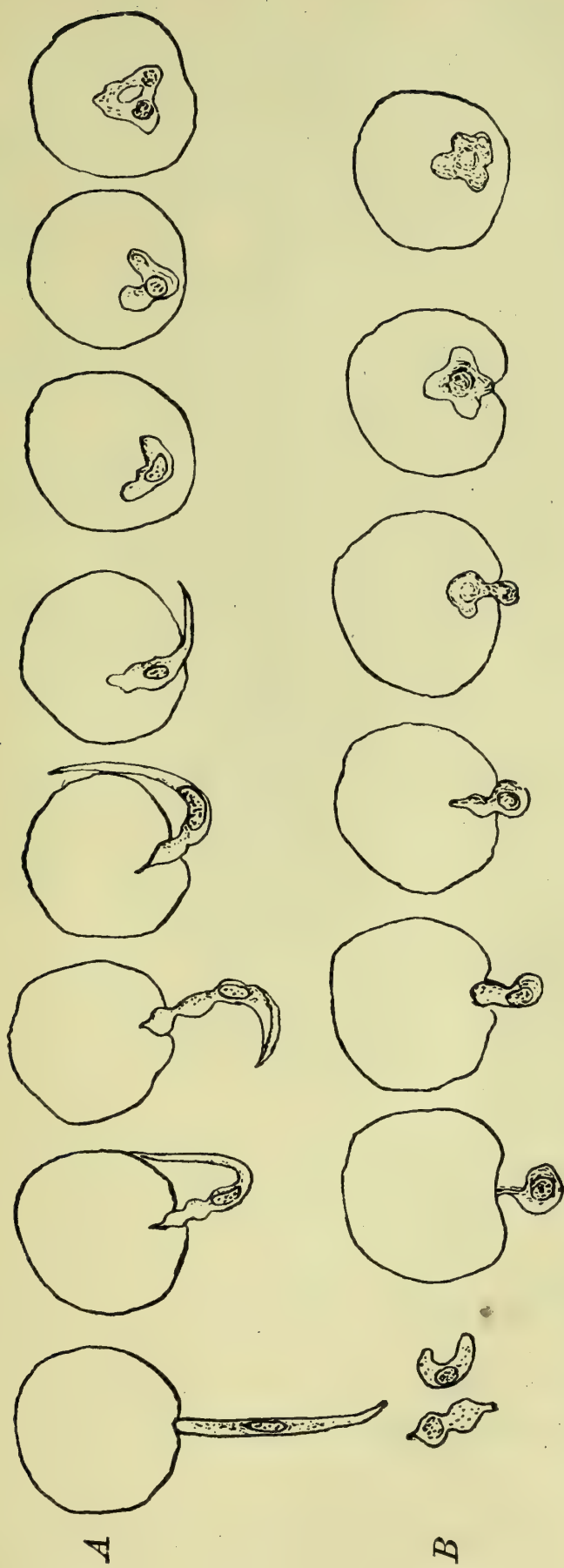


Fig. 4.—A, Entrance of the merozoites. B, Entrance of a sporozoite into a red blood corpuscle and transformation of the same into a schizonte. (After Schaudinn.)

following the nomenclature as given by Schaudinn, which considers the names employed by the different investigators, we obtain the following review:

The malarial parasites form the genus *plasmodium* with the three species:

1. *Plasmodium malariae* = quartan parasite.
2. *Plasmodium vivax* = tertian parasite.
3. *Plasmodium immaculatum* = tropical fever parasite.

The cycle of development of the malarial parasite is a twofold one:

1. A non-sexual one taking place in the blood of man—schizogonia (monogonia);
2. A sexual one occurring in the stomach of the anopheles—sporogonia (amphigonia).

The youngest parasites present in the blood corpuscles are either merozoites (monontes) resulting from the segmentation of schizontes (adult parasites) or filiform sporozoites produced by sporogonia.

The young parasite supplied with a nucleus rich in chromatin, assumes a ring-shape in that it develops a vacuole which serves for the enlargement of the surface of the body, and which Schaudinn considers to be a nutrition vacuole. With a gradual increase in size, the parasite which is to be designated as schizonte devours the hemoglobin of the red blood corpuscle, transforming the same into pigment, melanin. When full-grown, a constriction of the nucleus takes place, and it disintegrates into a number of particles—the merozoites which again enter the blood corpuscles.

This process is more or less frequently repeated in the same manner until “the body begins to react to the parasites.” Then the merozoites no longer become schizontes, but gametes, sexual forms; some of them large, with markedly granulated, easily stainable plasma—the female gametes, macrogametes; the remaining ones slightly smaller(?), not granulated, difficult to stain, containing much chromatin—the microgametocytes. The duration of the development of the merozoite into a gamete is twice as long as the duration of its development into the segmentation form.

The male parasite, the microgametocyte, produces in the stomach of the anopheles the microgametes (flagella) which fecundate the female parasite, the macrogamete. From the fecundated macrogamete develops the ookinete (vermiculus) which enters the wall of the stomach and develops there into an oocyst or capsule (the coccidium or the coccidia-like body). The oocyst divides into sporoblasts from which, finally, the sporozoites (crescent germs, filiform germs, germinal rods or threads) develop. The mature cysts rupture and discharge the sporozoites into the celom of the mosquito. These latter accumulate in the poison glands, especially in the middle lobes of the same, and are then transmitted into the skin of man by the sting of the anopheles. They subsequently enter the blood corpuscles and then multiply further by schizogonia.

If the gametes do not enter the body of an anopheles but remain in the blood of man, they are capable (the females, according to Schaudinn), by a parthenogenetic process of segmentation, to give rise to merozoites which then produce the recurrences of the attacks.

MORPHOLOGY AND BIOLOGY OF THE MOSQUITOES

After having determined that the species *anopheles* is of conspicuous importance in the origin and dissemination of malaria, it is also of special interest to the physician to become familiar with the morphological and biological peculiarities of this variety of mosquitoes, so that he may be able to distinguish it from other mosquitoes which are not concerned in the trans-

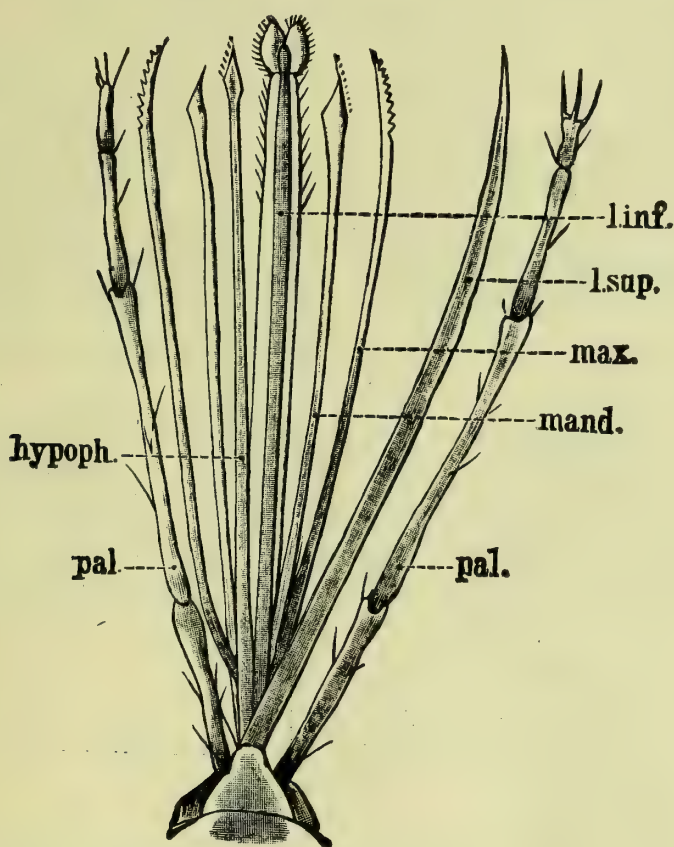


FIG. 5.—STINGING APPARATUS OF THE MOSQUITO.

l. inf., lower lip; *l. sup.*, upper lip; *hypoph.*, hypopharynx; *max.*, maxillæ; *mand.*, mandibles; *pal.*, palpi.

mission of malaria. We shall, therefore, briefly outline the principal characteristics which distinguish the individuals of the variety *anopheles* from other mosquitoes.

The family of mosquitoes is divided into three genera: *Aedes*, *anopheles*, and *Culex*, of which the genus *aedes* may be left out of consideration as it does not occur in Europe.

The individuals of the genus *anopheles* can, in all stages of their development, be easily distinguished from the individuals of the genus *Culex*.

Each mosquito consists of head, breast and posterior body. The breast carries two transparent wings with radial venation, and two posterior wings that have degenerated into small balancers. The wing veins are covered with scales which are more densely arranged at some places and form darker colored, peculiar areas.

The six, conspicuously long and thin legs consist of thigh, shin, and the five-membered foot.

The head of the mosquito carries, besides the two large eyes, two feelers, two labial palpi and the sucking and stinging apparatus. The lower lip, with the upper, forms the proboscis, haustellum, in which are enclosed as stilets the knife-like mandibles, the serrated maxillæ and a process of the lower lip, the hypopharynx (see Fig. 5).

At the tip of the hypopharynx there opens a fine canaliculus which passes through the latter and represents the excretory duct of the large three-lobed salivary gland. The digestive tract consists of an anterior, central, and posterior portion. The anterior portion consists of the pharynx and the esophagus, the latter presenting a large ventral, and two smaller, lateral sacculations, the suctorial stomachs. The central intestine consists of the anterior narrowed cervix of the stomach and the stomach proper, the posterior intestine of three parts, the ileum, colon, and rectum. The stomach proper commences at about the end of the second abdominal ring and extends to about the boundary of the fifth and sixth abdominal rings (Fig. 6). The stomach consists of an epithelial layer and two layers of muscular fibres which are held together by an elastic substance, an internal circular, and an external longitudinal, fibre layer.

The males and females are distinguished from each other in that the females possess short-bristled feelers, the males long-bristled ones, resembling a tuft of feathers. The male possesses only suckling organs, the female, besides, an apparatus enabling it to sting. Therefore, only the females are

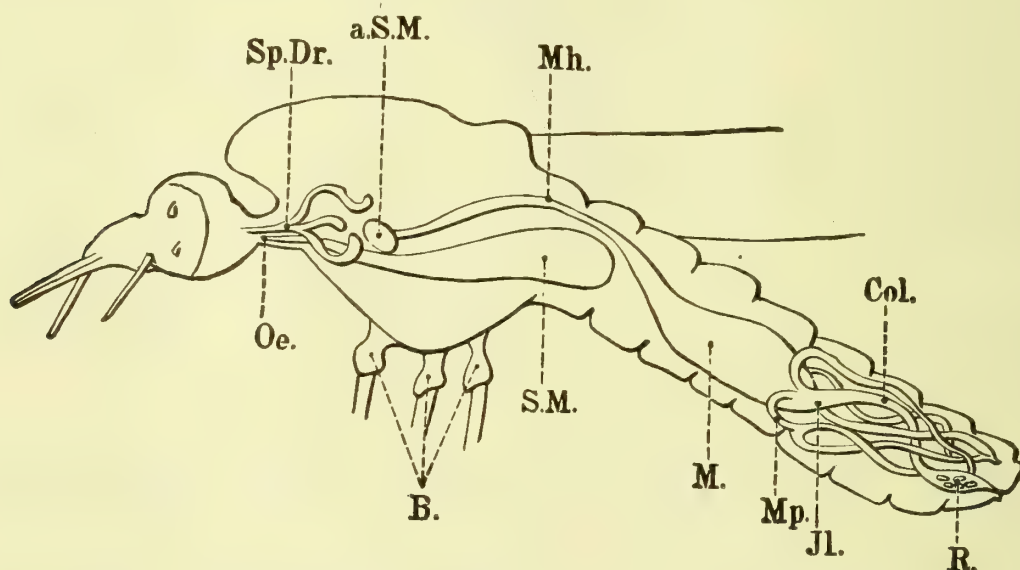


FIG. 6.—DIAGRAM OF A LONGITUDINAL SECTION OF THE ANOPHELES. (After Grassi.)

Oe., esophagus; *Sp.Dr.*, salivary gland; *a.S.M.*, accessory suctorial stomach; *S.M.*, suctorial stomach; *Mh.*, cervix of the stomach; *M.*, distended portion of the stomach; *Jl.*, ileum; *Col.*, colon; *R.*, rectum; *Mp.*, Malpighian vessels; *B.*, legs.

capable of penetrating the skin of animals or of man and sucking blood. Accordingly, the females alone are to be considered in the transmission of the germs of malaria.

The principal characteristic, distinguishing anopheles from culex, is the difference in the proportions of length of the proboscis and of the feelers. In the genus anopheles the feelers are equally as long as the proboscis; in the

genus *Culex* the feelers are shorter in the female, longer in the male, than the proboscis (see Fig. 7).

The wings in the *Anopheles* always show the above-described macules, which frequently vary in number and arrangement according to the genus, with the exception of one variety, the *Anopheles bifurcatus*.

Of the *Culex* varieties only the *Culex anulatus* has four spots on the wings, the same as the *Anopheles maculipennis*. The former is also distinguished by

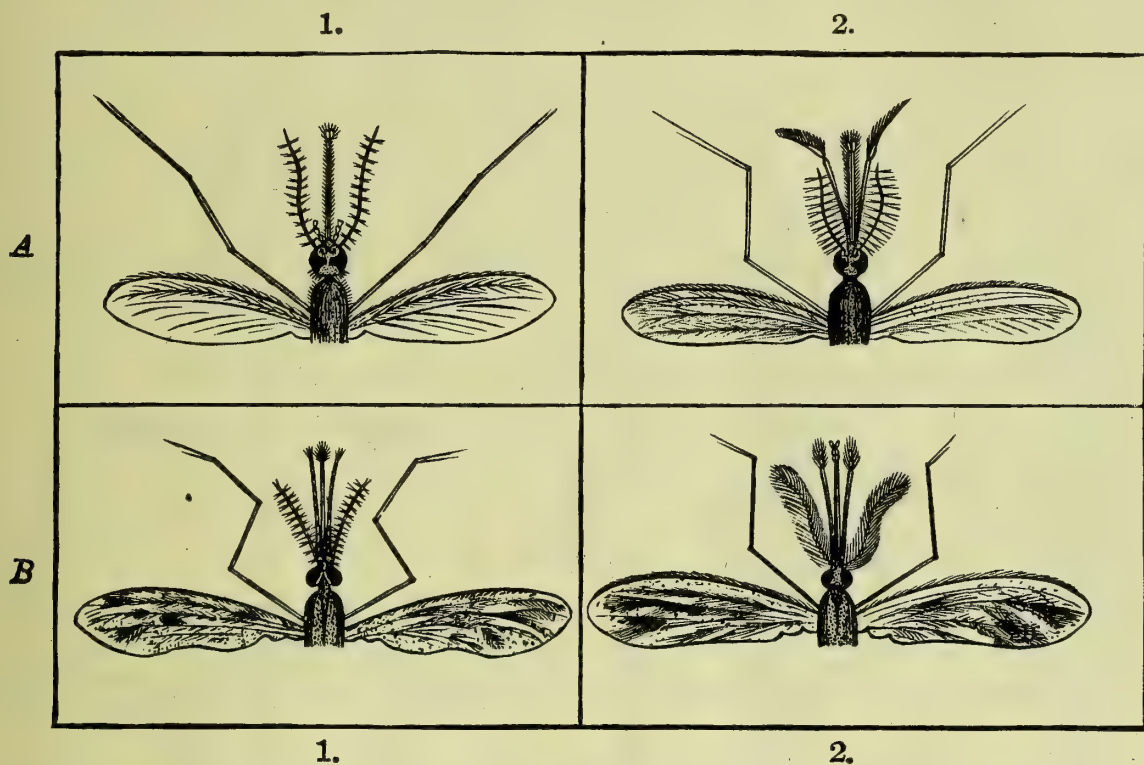


FIG. 7.—A, *Culex pipiens*: 1, female; 2, male. B, *Anopheles claviger*: 1, female; 2, male. (After Kerschbaumer.)

the yellowish-black striping of its legs so that thus both genera can easily be distinguished one from another, aside from the above-mentioned difference in the length of the palpi.

Besides, a difference between *Culex* and *Anopheles* can be observed at the first glance by the attitude they assume when on a vertical or horizontal plane. The *Culex* appears curved; head and proboscis are bent anteriorly, the posterior part of the body is approached to the basis, so that the body forms a distinct angle with the same (Fig. 8).

The *Anopheles* appear straight, the posterior part of the body points away from the base and forms an almost straight line with breast, head, and proboscis, so that it stands out from the base in a more or less acute angle. The first two pair of legs rest upon the base, the third pair is away from it and is suspended in the air. On the other hand, the third pair of legs in the *Culex* is bent upward. The space between the sitting *Culex* and the base is but narrow, whereas it is wide between *Anopheles* and base (see drawing).

The females lay their eggs upon water. The eggs of the *Culex*, 200 to 400 in number, are cone-shaped, rounded, spherical at the base (Fig. 9), 0.7. mm. long, and are deposited in the form of small heaps which bear a certain resemblance to the feces of mice.

The ova of the *Anopheles* are boat-shaped (Fig. 9, A, B, C, D), slightly

thicker at one pole, 0.8 mm. long, neatly latticed at the surface, often with dark maculæ, and surrounded with a membrane, the so-called exochorion, which extends from one pole of the ova to the other and is slightly broader in the centre, bordering on the right as well as on the left upon a small, air-containing space which is of importance for swimming. The female of the anopheles lays about 150 ova either in the form of ribbon-like parallel rows or in the shape of neat, stellate figures (see Fig. 9, A, B, C, D).

The dark-colored larvæ pass from the ova about two to three days after the ova have been deposited.

The larvæ of the anopheles are in part greenish, in part brownish or reddish. Immediately at the base of the shield of next to the last dorsal ring there open two stigmata. The larva directs the abdominal end toward the surface of the water and lies parallel to the same.

The larva of the culex possesses a respiratory tube at the posterior portion of its body, at the tip of which are two stigmata through which it takes the

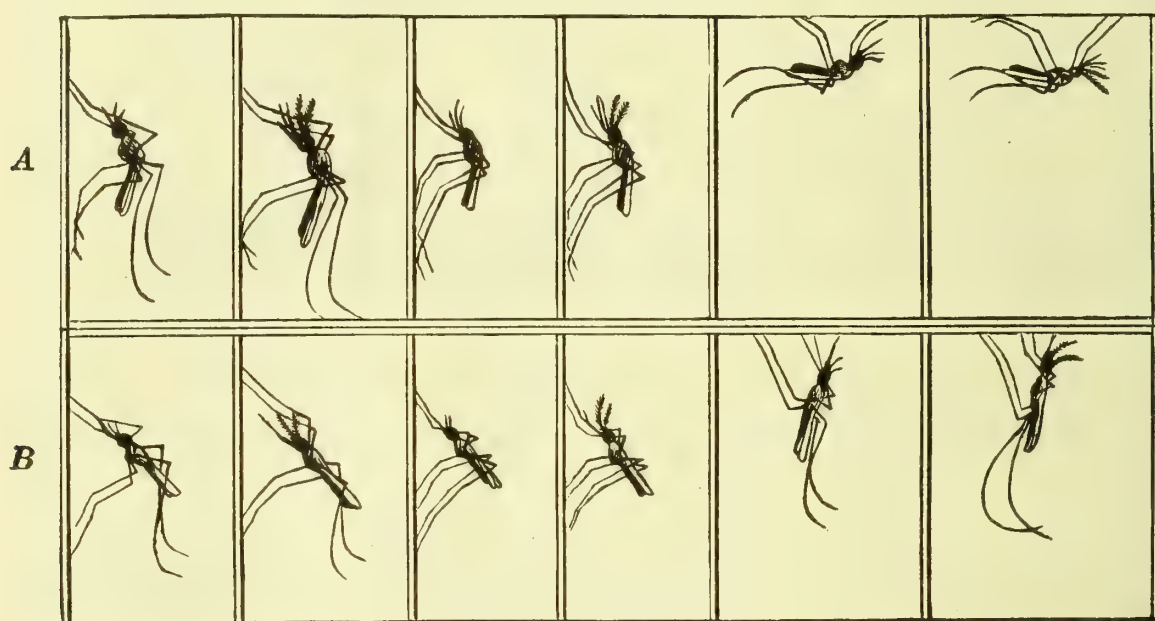


FIG. 8.—A, *Culex pipiens*; B, *Anopheles claviger*. (According to Kerschbaumer.)

air. The larva places the stigmata at the surface of the water and hangs almost vertically in the water (see drawing).

The larva sheds its skin four times. Each shedding of the skin is followed by the appearance of a larger and more pigmented larva, its size is 1, 3, to $4\frac{1}{2}$ to 7 and 9 mm. If the larvæ fold the stigmata, their specific gravity becomes greater than that of the water and they sink to the bottom. The diving may also be accelerated by active movement. If the larva attempts to rise to the surface, it accomplishes this by lateral beating with the posterior part of its body. According to Kerschbaumer, the larva from time to time goes to the bottom there to deposit its black, cylinder-shaped, or spherical excrements.

After the larva has ceased to grow it also ceases to eat. It then stands horizontally with the back of the thorax toward the surface of the water, it tears the cover of the thorax and from this slit the chrysalis escapes which is distinguished by two respiratory horns. The body of the chrysalis has the form of a laterally flattened sphere to which the freely movable posterior part

of the body is appended as a tail-like attachment. Two dark punctiform eyes are noted at the anterior part of the sides of the body. The chrysalis does not take any food (see Fig. 10, A_1 and B_1).

The chrysalis of the *Culex pipiens* and that of the *Anopheles claviger* are distinguished by two characteristic signs. The chrysalis of the former genus is possessed of long, very curved respiratory horns, with oval, much bent, serrated mouth openings, and narrow, long caudal fins. The chrysalis of the second genus is possessed of short, straight respiratory horns, with wide circular openings and broad circular fins. "The *Culex* chrysalis has trumpet-like

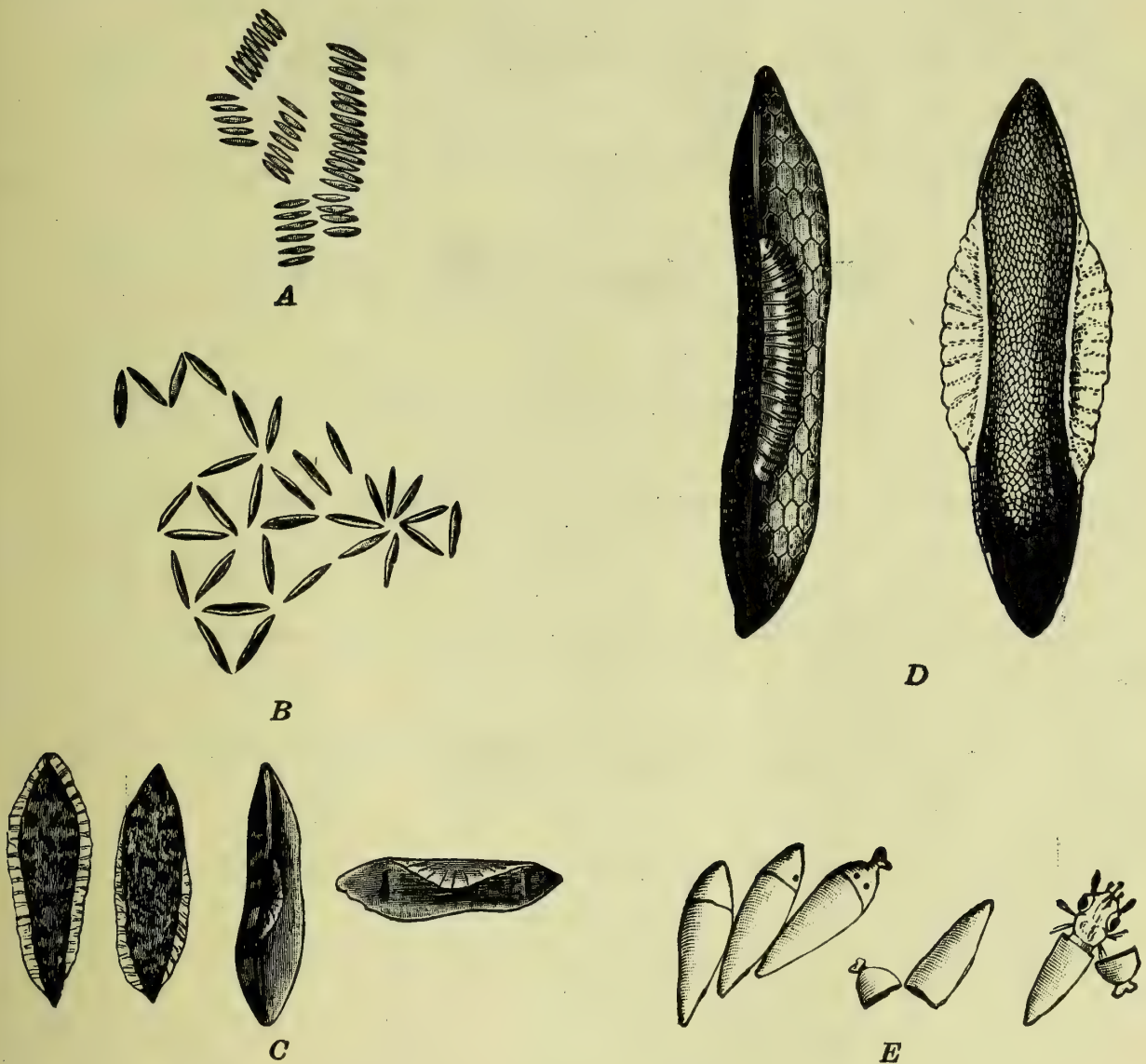


FIG. 9.—A, B, C, D, Ova of the *Anopheles*; E, Ova of the *Culex*.

ears and narrow rudders; the *Anopheles* chrysalis has funnel-shaped ears and rudders" (Kerschbaumer).

From the chrysalis develops the fully mature winged insect, the imago, in the manner that the chrysalis stretches itself horizontally at the surface of the water and bursts at the dorsal part which is leaning against the surface of the water. The imago rises from the slit with its middle body and head, then pulls out the forelegs and places them laterally upon the water, now also to free the posterior part of the body. The newborn imago rises, rubs the legs upon one another and with them cleans the feelers, proboscis, and wings.

The duration of development from the ova to the winged insect is about three to four weeks for the *Culex pipiens* at a temperature of about 59° to 68° F.; about two weeks at 68° to 77° F.; about one week at 77° to 86° F.

The duration of development is about one-fourth to three-fourth times longer than in the *Anopheles*. No development takes place under 53.6° F.

The males perish late during the autumn. The fickle-mated females hide in quiet protected places, stables, cellars, feed-lofts or haystacks and pass into a kind of hibernation from which they are awakened by the mild winds of spring. They now attempt to suck blood to develop the ova, to deposit them

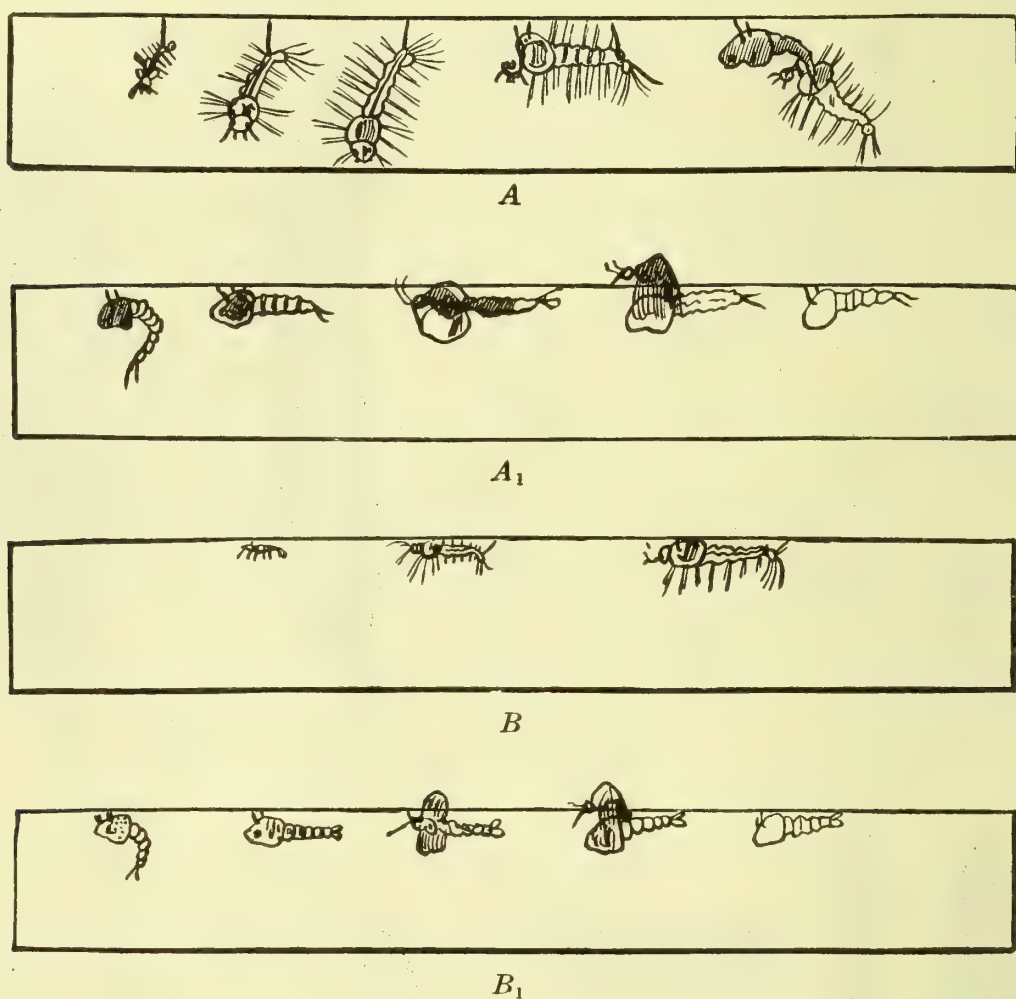


FIG. 10.—A, A₁, *Culex pipiens*; B, B₁, *Anopheles claviger*. (After Kerschbaumer.)

upon water surfaces which are situated in the rays of the sun and are above 50° F. during the course of March.

The first generation of the winged insects appears in April, mostly during the latter half of the month.

The *Culex pipiens* is said to furnish seven generations from the middle of April to the end of October; the *Anopheles claviger* four generations from the beginning of May to the middle of October. Kerschbaumer calculates the number of female progeny resulting from one hibernated *Culex* female to about one million billions, and from *Anopheles claviger* to about thirty-one millions.

The *Anopheles* are decidedly nocturnal insects. They usually sting only between sunset and sunrise, however, not exclusively. It has been frequently observed that they also sting occupants of rooms during daytime. They take

the blood from many warm-blooded creatures. They are, therefore, by no means restricted to man alone. Further logical details will be considered later on.

IS THE MOSQUITO THEORY IN HARMONY WITH ALL FACTS OF THE ORIGIN AND PROPAGATION OF MALARIA?

After the development of the mosquito theory has been followed from its beginning to its final scientific foundations, we must concern ourselves more minutely with the solution of the question: Is this theory then in accord with all the facts which have been determined by countless observers in the course of centuries regarding the origin and dissemination of the disease?

It is a fact that malaria preferably occurs in such districts in which various kinds of surface accumulations of water are present. As the larvæ of the mosquitoes require water to develop, the marshy character of most malarial districts is thoroughly in harmony with the mosquito theory.

The history of malaria teaches that by various modes of alterations of the soil, by earthquakes, by landslides, by construction of railroads, canals, etc., the development and extension of malaria may be promoted to an extraordinary extent. Lancisi as early as 1717 reports that, in Balneoregium, a landslide caused the water to rise at numerous places, that, subsequently, "*ingens culicum vis*" arose and the appearance of the inhabitants had changed in the course of a few years "*ex vivido ac nitido in flavum et pallidum.*" Earthquakes, in 1703 in Rome, in 1783 in Reggio, in 1828 in Palermo, and also in Peru, in 1835 in Amboina, were followed by a marked increase of malaria. The construction of Italian railroads which led through fever districts has given rise to extraordinary growth of the intensity of malarial affections so that many thousands of human beings have succumbed to it. The establishment of the harbor works at Wilhelmshaven was accompanied with an enormous increase of malaria. The introduction of malaria and the origin of enormous epidemics of malaria upon the Island of Réunion is known to have occurred in consequence of the coast districts becoming boggy, due to the clearing of the woods during the sixties of the last century. All these phenomena are easily explained by the mosquito theory, for all the above-named changes of the surface of the earth give rise to an accumulation of water and the mosquitoes increase wherever the formation of stagnant water and pools takes place.

The preference of malaria for soil containing clay and its absence in sandy regions, which has been demonstrated in many places in the world, is quite in harmony with the theory. This exception on the part of countries with sandy soil is particularly conspicuous in the coast districts of the North Sea.

Whereas the marshes which are rich in water and mosquitoes are fearfully devastated by malarial affections, they are almost entirely absent in adjacent localities with sandy soil; such observations were again recently made by Mühlens. The immunity of numerous localities on the Malabar coast in the Presidency of Madras is explained by the sandy soil prevailing there, according to the statements of Annesley, reported by Hirsch. The water is at once absorbed by the sand and, therefore, the larvæ of the mosquito cannot develop.

The immunity of many districts of calcareous, in contrast to those of volcanic, ground, are explained in the same manner.

However, it appears that a number of observations are not in accord with this theory, according to which, malaria occurs in a malignant form in mountain regions that are poor in water, and this form has been repeatedly described as *mountain fever*, *hill fever*. However, in all these cases it is a question of formation of the soil in which accumulations of water, especially during rainy periods, are found quite frequently, in which, therefore, mosquitoes are not absent.

It has been contended that there exist typical malarial regions in which no mosquitoes are present (Schwalbe has compiled quite a number of such statements), and, on the other hand, that mosquitoes may be numerous present without the existence of malaria.

The careful investigations which have been undertaken regarding the occurrence of malaria in regions that are without mosquitoes have led to the unquestioned result that these statements are not correct.

It has been learned but very gradually how to find the anopheles in their hiding-places, namely, their larvæ in the regions inhabited by them. Thus, for instance, in Kamerun the anopheles were not found at first, whereas, later, their presence was determined in various species. The belief that they were absent in the malarial regions of West Africa, in the Sierra Leone, has been destroyed by the English Niger expedition. Their presence could be determined only by the construction of artificial pools which were then utilized for the deposit of ova by the females of the anopheles which, otherwise, could not have been discovered. Schüffner was able, in this manner, to recover females of a special kind of anopheles which he had brought from the coast of Java to the interior and which had escaped there. It is a fact that, wherever endemic malaria is present, its transmitters, the anopheles, are found also. In those localities, however, in which anopheles could not be found either in the dwellings, in the dark huts of the natives, or in the stables of the cattle, their favorite abodes, or with the aid of artificial pools, and in which malaria was, nevertheless, recognized, it was not a question of endemic malaria but of malaria which the inhabitants had acquired elsewhere. Koch has reported quite noteworthy illustrations of this character.

That malaria may apparently be absent, nevertheless, in exquisitely malarial regions, has also been determined by Koch. In such cases the adults were healthy and free from fever, it is true; not so, however, the children who were affected up to 100 per cent.

The occurrence of malaria among crews of ships that had anchored in malarial regions in the neighborhood of land, without, however, a landing having taken place, is easily explained by the flying of infected anopheles from the shore to the ships. It has been contended that infections had also occurred on such ships as were anchored further away from the land than the anopheles were able to fly. The opinions have varied greatly in regard to the distance which the anopheles are able to cover. Some contend that they are only able to fly a very short distance; others, again, say that their flight might extend over many kilometers. Wenzel has observed that malaria occurred in Wilhelmshaven about five kilometers from the much infected harbor district.

Ambrosi and Riva have seen the anopheles display their activity in the Province of Palma four to five kilometers from the rice fields, the principal breeding places of the anopheles.

Of particular interest are the investigations of Grassi which he has undertaken in Norma, Sermoneta, and Sezze, villages situated on the hills opposite the Pontine Marshes.

In Norma, 343 meters above the level of the sea, malaria was said to be absent, whereas it was reported to be present in Sermoneta (about 257 meters) and in Sezze (about 319 meters), although less frequent than in the Pontine Marshes proper.

Malaria broke out, in 1899, about October 20th, not only in Sezze and Sermoneta, but also in Norma. In December of the same year Grassi found in all three of these places, but especially in the dwellings situated near the Marshes, numerous anopheles.

The breeding places of the anopheles in Sezze were water ditches which were supplied by springs, whereas this was not the case in Sermoneta and in Norma. Grassi, therefore, considered without doubt that the anopheles observed in the latter places originated in Ninfa which is only 24 meters above the level of the sea, i. e., below Norma, that, therefore, they had arisen 300 meters above the level of the sea. He believed that they succeeded in getting there by stages, following the numerous caravans which ascend daily, toward evening, to the above-named towns. The mosquitoes uninterruptedly pursue the travellers, as will be confirmed by every coachman who drives from the station up to Sezze. That the anopheles, and with them malaria, did not occur in Sermoneta and Norma until late in the year, in October, he ascribed to the fact that the inhabitants of the plains emigrate to the hills during this period and that now the anopheles, owing to the absence of proper winter quarters, retired from the plains to the inhabited towns and villages of the hills.

Grassi ascribed great significance to the passive dissemination of anopheles by vehicles carrying human beings or laden with hay or straw for the exceptional propagation of anopheles, several kilometers from their places of origin.

S. Cropper reports from Palestine, that larvæ of anopheles were carried several kilometers with the drinking water taken from cisterns, so that, in this manner, malaria arises in localities which are several miles away from the breeding places of the mosquito.

However, the anopheles, as a rule, remain in the neighborhood of their places of origin.

Also an important factor for the dissemination of anopheles is the wind, to which they are very sensitive. If this strikes them, they arise at once and fly toward protected places. The movement of the air is usually more active with their arising from the earth. This explains why one is more exposed to the stings of anopheles when remaining in the lower parts of the house than in the upper stories; hence, the popular old rule of not sleeping on the ground, but in elevated regions, in malarial places.

If a slight wind blows from the land it may carry anopheles to vessels and cause infections on them.

Nor can the occurrence of malaria on board ships during long voyages be

considered as an objection to the anopheles theory, because it has been shown that anopheles which have once reached a vessel may persist there for some length of time. Very interesting in this respect is a statement of Nuttall, according to which Roe has observed about a dozen foreign varieties of anopheles on a vessel quarantined in New York harbor.

The duration of life of the anopheles varies. It has been ascertained experimentally that it may amount to seven weeks; it may be a still longer one in the non-hibernating females.

A peculiar observation which is a suitable explanation of the nonappearance of malaria in places with anopheles, in spite of the introduced cases, was made by Grassi in water springs which are in the neighborhood of the Serino springs which supply water to the city of Naples. There he found very numerous anopheles, but mostly in the stables, few in the dwellings; this condition did not correspond with the fact that malaria is rare there although it is often introduced. How was this disproportion to be explained? The anopheles were not immune to the malarial parasite of these regions, as he was able to prove by experiments. Necessarily, another cause was active. He found it in the relatively low temperature which prevailed in St. Lucia di Serino, which was situated at an altitude of 400 meters, surrounded on all sides by high mountains. Owing to the low temperature, according to the opinion of Grassi, the anopheles mostly hide there in the stables which are always warm and, therefore, preferably sting cattle, horses and pigs, and only rarely human beings. He made the same observations also in Alserio (Brianza) and in Noe in Sala-Braganza in the Province of Parma. In the cool and airy, highly elevated regions, the anopheles are found only in stables and do not bite human beings. Accordingly, these districts are free from malaria. In the warmer lowlands, however, they torment humanity greatly and much malaria is found there. He believes, therefore, that anopheles may be considered as the true indicators, "*la spia vera*," of malaria only in those regions in which the temperature is very suitable for the occurrence of malaria.

Very remarkable, and apparently in opposition to the anopheles theory, is the occurrence of paludinal regions with numerous anopheles, and occasionally introduced cases of malaria, or even cases of the disease which arise there, without the development of malaria. Celli has reported on numerous and extensive districts of this character in Tuscany. In many of them even severe malaria was prevalent formerly; however, it has disappeared without special hygienic improvement of the ground, extensive administration of quinin or acquired immunity of the population being responsible for the condition. He now believes that these phenomena might depend upon certain qualities of life of the anopheles present in these districts. In numerous experiments with anopheles from these regions, he found that only a small percentage (3.5 per cent.) sting human beings, quite in contrast to the anopheles from the Tuscan and Roman Maremmas, and of those anopheles which have bitten man, only a small percentage (2.8 per cent.) can be shown to be infected. It was a question, therefore, of anopheles which did not bite man and which did not become infected, and, consequently, were not capable of disseminating malaria.

Similar conditions were quite recently observed by Schüffner in Sumatra. Whereas severe malaria prevails in the coast regions, especially in the Canton Pandjang, the interior is entirely free from the disease. Schüffner then found several varieties of anopheles which were distinctly different from one another, a light-brown species and a black one, which he has described more minutely as anopheles I (I^a) and II.

He was not able to cause anopheles I and I^a to sting, whereas he accomplished this very easily with anopheles II, the latter were even distinguished by a peculiar avidity for blood. It does not cease to suck when it is completely filled up, but it continues, rinses its intestinal canal with the blood and afterwards even passes the sucked blood droplet after droplet per anum. "A hand upon which fifteen or twenty of these insects have sucked, with all its droplets of blood, looks as though hit by a dense load of shot." Schüffner succeeded excellently in following the exogenous development of the malarial parasite in these anopheles. This same variety of anopheles occurs also in the interior of the country, but there the developing insects are much smaller and weaker than those that have grown upon the coast. Schüffner writes: "Copulation probably occurs during the first day of life as a winged insect, and many of the mosquitoes even attempt to sting. However, an attempt is all they are capable of; they are not able to penetrate the skin, the body remains empty and the result is that none of the insects live beyond the second day." According to Schüffner, anopheles is an obligatory coast insect. It does not thrive in the interior. Introduced into the interior, it is true, it is able to perpetuate for some time if it finds a favorable soil; however, it degenerates after several generations. Already the first generation had less avidity for blood, the second one was satisfied with filling its body with blood, the fourth one was no longer able to eat, and perished rapidly. Anopheles I, which is less dependent on the coast also degenerates further toward the interior. Schüffner attributes the degeneration of the anopheles to the altered chemical and organic conditions which the larvæ find in the pools of water of the interior, and also to the increasing prevalence of the natural enemies of the anopheles.

From this state of affairs a condition results which, according to Schüffner, might be called a sort of immunity of the country to anopheles. Similar observations have been made in Bengal by Stephens and Christophers. They did not succeed, as little as did Ross, in infecting a variety which is now called anopheles Rossi, so that it is demonstrated that not all the species of anopheles participate uniformly in the propagation of malaria.

Extremely interesting are the results of investigations which were undertaken by Dönitz with the enormous mosquito material collected by Koch on his travels and by the Governor of Holland at his suggestion in Dutch India.

Apart from the finding of numerous, until then unknown, varieties of anopheles, Dönitz has determined the important fact that there are large districts, namely tropical highlands of the Pacific Ocean, distinguished by their abundance of water and their luxurious vegetation, in which anopheles and also malaria are entirely absent, such islands as Samoa, the Island Matupi in New Pomerania, the Sassi Islands between New Guinea and New Pomerania, the Marianne Islands, and the Carolines. He then, by reason of his studies has arrived at the conclusion that something takes place in those regions,

which, up till this time there has been no opportunity of observing: The immigration of existing zoological species into new districts, and, in the train of it, the propagation of the malarial disease. Thus, he believes that a species, which he has designated *anopheles vagus*, is in the act of migrating from West to East. This *anopheles* has succeeded in travelling from the Island of Celebes, where it is the only representative of *anopheles*, to Ceram, and even in most recent times to New Guinea where only one kind, the *anopheles punctulatis*, was prevalent until then. Dönitz believes that they are very apt to be carried away by the commerce of the natives and traders who keep rain water in their boats, regularly hiding larvæ of *anopheles* in the water.

The more the studies of *anopheles* and their relations to malaria broaden, the more interesting and important are the results. This much, however, appears even now from the countless observations which have been made in the most various localities of the world, that the correctness of the postulate—where there is malaria there are also *anopheles*, without *anopheles* no malaria—can no longer be doubted.

And yet there is a weighty objection which has been raised against the transmission by *anopheles* and which renders the latter unacceptable at the first glance. This is the objection: Epidemics of malaria have been observed during remarkably raw, cold weather in spring, in fact, even during severe cold in winter, during which times no mosquitoes exist. Hirsch in his historico-geographical pathology, states as follows regarding this point:

“Frank reports: *vidi plures Vilmæ febres intermittentes caput extulisse mense Februario, thermometro Reaum. viginti et ultra frigoris gradus indicante*”; an epidemic of malaria was present in the winter of 1841–42 during severe cold, in Kasan, according to the statement of Blosfeld; Myersohn writes from Astrachan: “It is a fact that the fever is present even when the thermometer shows 20° C. and colder”; and Walther notes from Kieff: “That in our (Russian) Eastern governments the epidemics of fever are manifest even when a rigid covering of ice is spread over nature, and which, if the statements which I had an opportunity of hearing are correct, attain a greater intensity than during the heat of summer, even with us a frost of from 10° to 20° C. does not protect from fever, as is proven by the serious deficiency of quinin during December and January, which had been consumed in the course of the year.”

There can be no doubt, therefore, that numerous cases of fever may occur in winter, yes, so numerous that we may speak of epidemics even if we are as skeptical as possible regarding such diagnoses. However, the assumption that these winter fevers are new infections, is very doubtful. All these winter fevers were preceded by numerous fevers during summer and autumn, as follows distinctly, for instance, from the statement of Walther regarding the quinin consumed in the course of a year.

The above observations do not contain any statements whether they referred to new infections or to recurrences. According to the experiences gained now regarding the appearance of recurrences, there can be no doubt that the winter fever, in the great majority of cases, is nothing else than a recurrence which follows upon infections during the previous epidemics.

Manson reports a case of experimental malaria in which a recurrence took

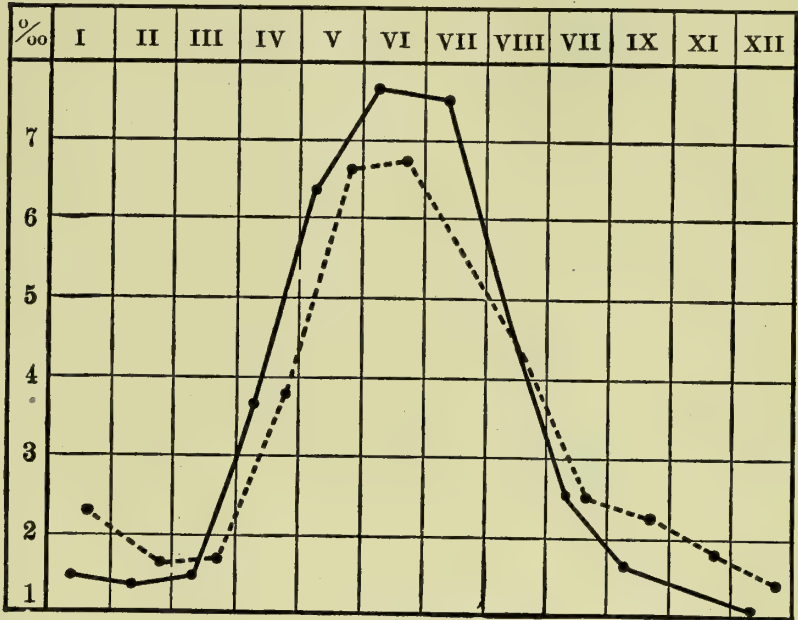
place after nine months. Schoo, who has carefully studied this question in his patients in Krommenie, determined in thirty-eight persons an interval of the first infection, a recurrence varying between one hundred and twenty to four hundred and twenty-three days. And even if a number of newly infected individuals has been among the latter, the fact remains that months may intervene between infection and recurrence. If, therefore, numerous affections have occurred during the course of a year during the warm season, numerous cases will occur also during the subsequent cold period. Many cases might also be conceived as infections with a very long period of incubation, the occurrence of which we shall discuss later on.

Therefore, it is no longer possible to quote winter epidemics as a proof against transmission of malaria by anoph-eles.

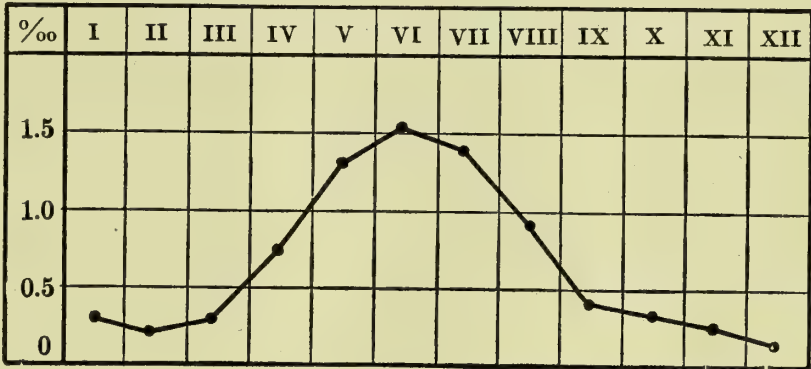
The only objection now remains, that in temperate climates, thus especially in Germany, the malarial curve shows an abrupt rise as early as in March, to culminate in May, latest in June, and then to decline just during that season which is most favorable for the development of anopheles.

Especially E. Grawitz has emphasized that numerous statistics, thus those of Wunderlich, of the Jacobs Hospital, of Leipzig, that of the Prus-

sian army, and especially that of the First and Fifth Army Corps stationed in East Prussia and in Posen, in the most eastern provinces of the empire, prove (Fig. 11), in a quite indisputable manner, that a very extensive infection with the germs of malaria occurs even at the beginning of spring, during March and April, at a time during which, just in these districts, there can only be a question of mosquito bites. Grawitz says: "For, with the climatic conditions in the eastern parts of the monarchy, a 'playing' of the mosquitoes may occasionally be noted in the open on rare sunny days toward the end of March and April, but a 'biting' of the insects during this time is almost excluded;



No. 1.



No. 2.

FIG. 11.—MALARIAL AFFECTIONS OF 1884 TO 1888.

Curve 1 is that of the First Army Corps, the dotted line that of the Fifth Army Corps. Curve 2, that of the entire army. (After Grawitz.)

finally, the temperature of 30° C., which is necessary for the development of the parasite in the body of the mosquito, is only exceptionally present in our regions at this time of the year. On the other hand, especially during the

hot months, in July and August, when the insects sting most intensely, we note that the curve falls abruptly, although just during these months and in September the soldiers are most exposed, during the manœuvres, to the bites of the mosquitoes.”

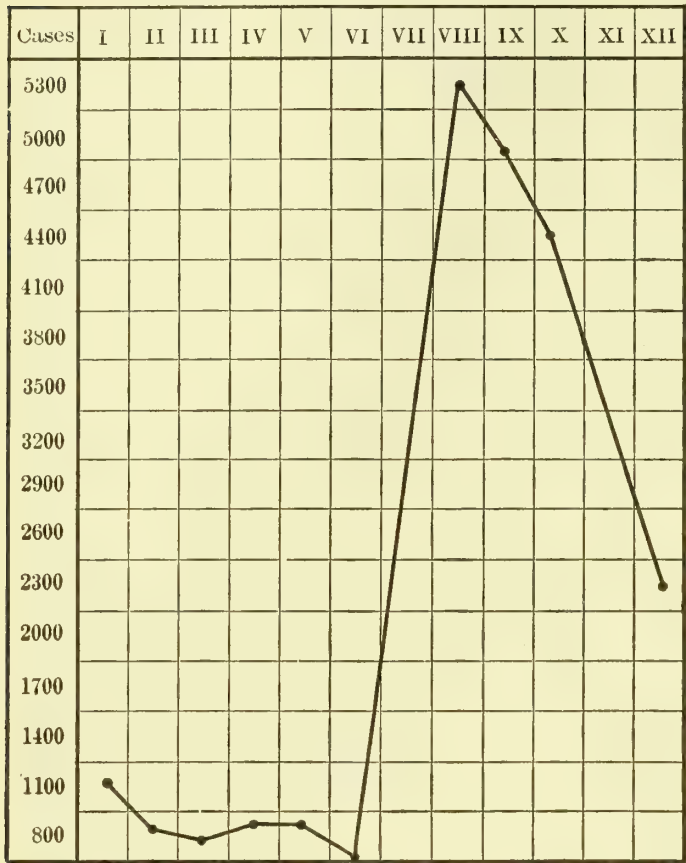
These statements of Grawitz, convincing as they may appear at the first glance, are, nevertheless, not capable of shaking the theory of the transmission of malaria by anopheles.

The malarial curves of moderate climates mostly do not conform with malarial curves of tropical and subtropical countries, for instance, with curves obtained with an extraordinary uniformity in numerous regions of hot central Italy. These curves show the abrupt rise as occurring toward the end of June until the beginning of July, the acme is reached in August, and the fall takes place in September and October, until November, according to the temperature remaining high for a longer or shorter period of time (see the curves in Fig. 12).

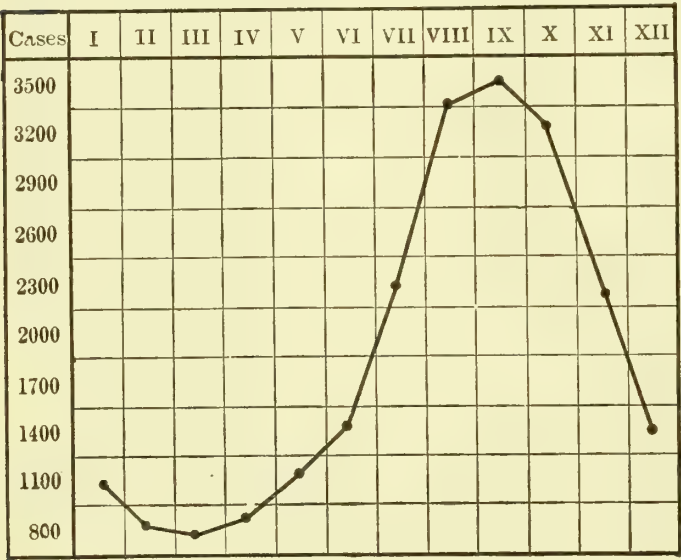
How is this varying, apparently paradoxical, conduct of malaria to be explained?

Koch, who observed, in Grosseto near Rome, the development of the epidemic in spring (the first appearance of the new cases), recognized with acute discernment that their appearance was in relation with the rise of temperature,

that a rapidly growing increase of freshly infected cases of malaria did not take place until about three weeks after the temperature had reached such a height as to remain everywhere in closed rooms, even at night, at 24° to 25° C. Then only he found mosquitoes which presented coccidia-like spheres in the



No. 1.



No. 2.

FIG. 12.—Curve 1, Epidemic type of lower Italy. Curve 2, Epidemic type of upper Italy. (After Celli.)

walls of their stomachs. He concluded, accordingly, that the above temperature is necessary to the development of malarial germs.

However, in regard to Koch's observations concerning malaria in Grosseto, it was principally the tropical form which furnished the basis of his investigations. As in our latitudes (Germany) the form caused by the small parasite does not occur, the question arises whether these forms might not require a higher average temperature for their development in the anopheles than that of the parasite of our domestic tertian fevers. Naturally, this question would only be decided by experiment. Van der Scheer and Bernedis van Berlekom have undertaken interesting investigations regarding the development of the malarial parasites in Middelburg.

They found no capsule in three anopheles which had sucked blood on the first day of their experiments when the temperature fluctuated between 14.5° and 16.5° C. Of five mosquitoes which had sucked during the following night when the temperature had risen to 18° to 21.5° C., four were infected. During the period of twenty-one days, from July 24th to August 15th, which was necessary for the development of the sporozoites, there occurred a space of time of thirteen days, from July 30th to August 12th, during which the daily maximum temperature did not rise above 21° C. and during which the minimal temperature was always below 15° C.

Schoo studied the development of the tertian parasite in the anopheles still more closely in Krommenie, in that he caused a number of anopheles to suck blood from patients with many gametes, and then kept the insects at various temperatures in the incubator. The capsules developed vigorously at 25° C.; the salivary glands contained sporozoites fourteen days after the infection. The development was still more rapid at 30° C.; mature capsules were present even after ten days. At 18° C. the capsules did not mature until after eighteen days. A fall of the temperature, about three days after the infection, to 10° to 15° C. during twenty-four hours did not prevent the development. During an experiment which was undertaken from the fourth to the sixteenth of September in the open air and in which the maximal temperature only on four days rose to 20° C., and above, whereas on the remaining days it fluctuated between 14° C. and 16° C., while the minimal temperatures were once 9° C., five times 10° C., three times 13° C., once 14° C., once 16° C., and once 18° C., ten of the twelve anopheles showed large, but as yet immature capsules, on the twelfth day. Of twenty-six anopheles which were permanently kept at a temperature of 15° C., none were infected after twelve days. There can be no doubt, after these experiments, that the parasites of our domestic tertian fevers may still develop in the anopheles at temperatures of less than 20° C., even when the minimal temperature is at times only 10° C. Such temperatures, however, are quite regularly present with us in heated rooms during spring. Enticed from their winter abodes the anopheles are regularly present, year after year, either as early as February or surely during March and April. Schoo observed in Krommenie, in the early spring, in 1901, as early as February, the female anopheles which had hibernated in cellars, pan-tiles, cattle and pig pens, take wing to deposit their ova. If they then find individuals who suffer from recurrences of the previous year (and these relapses of tertian fever occur particularly in the early spring with us), they

infect themselves with the gametes. They now remain in the warm houses near the stoves, in the upper parts of the rooms. There the temperature is sufficiently high to develop the sporozoites. But before they perish, they are still capable of infecting numerous individuals by their further acts of sucking. The new breed of anopheles, which grows up in February and March under favorable conditions, may be sufficiently developed even in April to

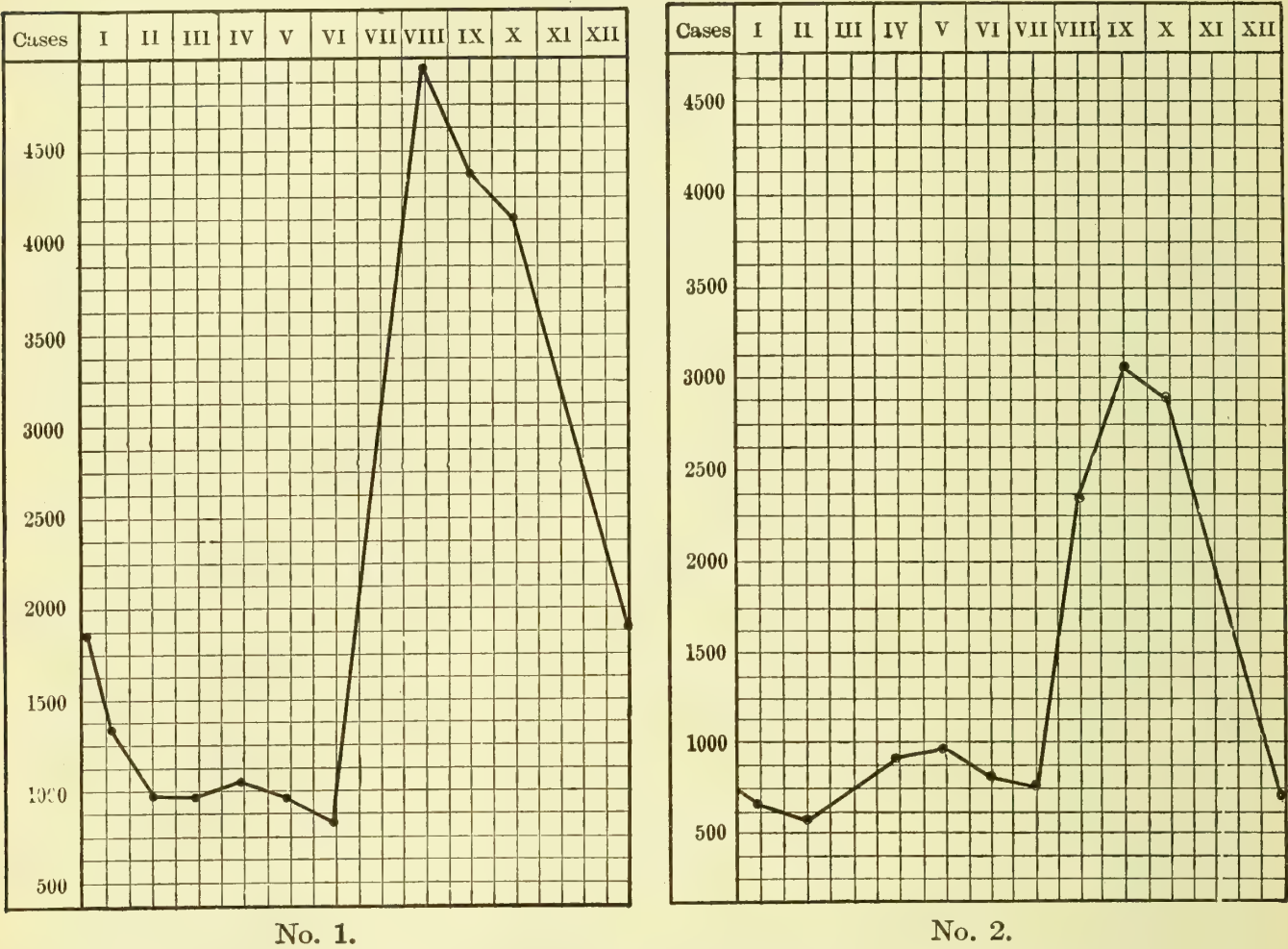


FIG. 13.—Curve 1, totals of the monthly additions of malaria cases in the hospitals of Rome, during the years 1892 to 1896. Curve 2, totals of the monthly additions of malaria cases in Wilhelmshaven during the years 1860 to 1869 (Wenzel). (After Martini.)

sting. Accordingly, the number of affections will increase during April and still more during May.

As the fresh cases are probably at once treated with quinin and as the recurrences of the previous year become continually rarer, the number of new affections will decrease during June and remain small.

The malaria curve in Germany is, therefore, dependent, in the first place, upon the variety of the parasites, tertians; further, by the occurrence of relapses in the early spring; then, by the early days of spring; but, especially, by the climatic conditions of the dwellings, which allow the infected anopheles to mature the parasites during the early spring.

Martini has recently furnished a very good proof that the explanation of Koch of the course of malaria with us is actually the correct one. Among the domestic curves was one which differed absolutely from the others, which, however, showed a course which conformed exactly to those of Italy: the

curve of malaria in Wilhelmshaven from 1860 to 1869, during the first ten years of the existence of the town (see Fig. 13).

Martini, who during that period and later investigated the dwelling conditions of laborers in accord with directions from Koch, determined that during this period the laborers were mostly housed in straw-covered, unheated huts without attics. The temperature necessary to mature the sporozoites in the anopheles was not present during spring in these cold rooms of three meters' height. Therefore, the malarial curve did not show its maximum until late in summer, twenty to thirty days after continuous maximum of the external temperature, the same as in the Southern malarial districts.

On the other hand, Martini found that now these houses in which new malaria cases occurred in spring showed partly very remarkably high degrees of heat in their rooms, as he was able to determine by exact computations of the temperatures. Anopheles were found in the malarial houses during the entire year, but only in the cellars. They were not encountered again in the dwellings until the beginning of April. Three new cases of tertian fever were observed in such houses on March 24th, April 6th, and April 11th, and shortly afterward on April 12th and April 14th, a number of anopheles which had sucked the blood of these patients were caught in these houses. The sources of infection were patients living near by, who suffered from recurrences of the fever.

Thus, we may conclude with Martini, "the spring maximum of the malarial curve may be naturally explained, with the aid of the above observations, in our artificial summer climate, warmed by means of heating, by the instrumentality of the anopheles."

Besides, however, many early spring infections permit of still another explanation. They may possibly also be due to hibernated infected anopheles. For the question has by no means been decided as yet in a negative sense, whether fecundated and hibernated female anopheles which were infected late in autumn, when they suck blood during early spring to develop their ova, are still able to infect by means of this act of sucking.

It does not require any further comment that the countless epidemiological observations regarding the occurrence of severe epidemics of malaria after hot, damp summers or after hot, dry summers with damp and warm autumns, regarding the onset of the epidemic after the beginning of the rainy season in the tropics, its abatement at the height and its renewed flaring up toward the end of the same, the complete cessation during the dry season in the tropics, as, for instance, on the Senegal and, with us, during winter, etc., can all be explained without difficulty by the corresponding influence exerted upon the anopheles.

COURSE OF THE DISEASE

Malarial diseases have a distinct period of incubation. It has been possible to ascertain this period with great accuracy in a large number of cases, in expeditions to malarial countries, in affections of marines who had been ashore for only one day. Thus, Navarre reports that he observed when at sea, severe attacks of fever in a number of men, twelve days after they had left Dakar, where the men had been ashore for only about three hours. Marchoux reports

that the substitutes that arrive at the Senegal in small troops are never affected earlier than fourteen days after their arrival. The disease generally sets in between the fourteenth and sixteenth days. The incubation period varies in Kamerun, according to the observations of F. Plehn, between eight and fourteen days; Ziemann was able to assume with some probability an incubation period of ten, or even of eleven days in two cases.

The incubation period of our domestic malaria, tertian fever, has been determined by Wenzel in Wilhelmshaven to be, on an average, also fourteen days. The incubation period of the quartan fever usually appears to be a longer one. These observations harmonize well with the periods of incubation which were observed in the numerous artificial inoculations of malaria from man to man, either by subcutaneous or by intravenous injections of malarial blood. The attacks occur at the earliest after five days—Panichi, who pricked his finger with a cover-glass smeared with the blood of a patient suffering from estivo-autumnal fever, had a severe attack even after five days—frequently after ten to fourteen days, and sometimes even still later, after three weeks. However, in these cases the attacks proper were preceded by slight febrile movements. Very long periods of incubation, forty-seven, yes, even sixty-six days, were observed in experimental quartan fever. It is quite conceivable that the period of incubation varies, as the number of germs which are introduced into the body during the various infections may fluctuate quite considerably. In natural infection, it is possible that the infected individual may be stung by one, or also by several, infected anopheles. Furthermore, the number of mature crescent germs which the infected anopheles transmit during stinging may vary considerably, according to the larger or smaller numbers of gametes taken in by the latter when sucking. Theoretically, the briefest possible period of incubation would be two days in tertian and tropical fevers, three days in quartan fevers. It would be possible to observe the same if the numbers of germs during the infection were so large that their first sporulation would at once cause an attack. The cases of incubation of only forty-eight hours, which various observers claim to have ascertained, might be explained in such a manner. But in those cases in which as early as a few hours or twenty-four hours after the visit to a fever district, typical attacks with chills are said to have been observed, there was, owing to no microscopical examination of the blood, either a diagnostic error or a latent infection which had taken place at an earlier date and which was only produced by some noxa after the affected individual had reached the fever district. Such infections which remain latent for a long period of time, for several months, have been surely observed. Ferrus, Maillot, Braune, Fiedler, Vallin, A. Plehn, and others, have described cases in which individuals who have sojourned for some length of time in fever regions without ever having suffered from a typical attack, became typically affected after they had left the malarial district, after a voyage lasting several weeks, or even in their homes that were free from fever. The majority of these cases might probably be explained in that such persons actually suffered from slight attacks which, as they ran their course without any subjective symptoms whatever, were not noticed by them at all, that it was a question, therefore, of recurrences, which were produced by various influences reducing the former resistance of the body, such as

severe seasickness or violent refrigerations, as occur especially often in those returning from a tropical climate to colder zones.

Clinical symptoms may be entirely absent during the incubation stage. Often, however, there are certain *prodromal phenomena* noted, general lassitude, headache, loss of appetite, sensation of pressure in the gastric region, nausea, vomiting, constipation or diarrhea; phenomena which, especially when they are accompanied with febrile movements, suggest that a "gastric fever" is imminent. Pains and drawing aches in the limbs are also quite often combined with the gastric manifestations. Bronchitic symptoms become more prominent in some epidemics.

The *attack proper* of the fever usually begins with a sensation of great lassitude and with headache. The patients yawn often and stretch themselves. They begin to feel chilly, occasionally a cold chill passes over them so that they require warm coverings. The sensation of cold gradually increases to a typical chill, the teeth chatter, the body trembles, a marked sensation of oppression becomes manifest in the chest, the headache is intensely aggravated and, finally, the patients are shaken by violent chills. At the same time their appearance is markedly altered. The temporal grooves appear sunken, the nose pointed, the eyes deep-set, with dark borders. The lips and terminal phalanges show a bluish appearance. The skin is pale, waxy, and presents the picture of *cutis anserina*. The pulse is very frequent, small and hard; urination is frequent. The temperature during the chill rises abruptly four to six degrees and may advance as high as 105.8° F. Griesinger has observed even 106.7° F. It is reported that even 108.7° F. and slightly above this have been noted. The chill may be of very short duration or it may persist for hours. The *stage of heat* is ushered in by an alternation, after some time, with paroxysms of heat. The patient feels as though heat were rushing from the interior to the surface of his body. The skin begins to become flushed and again grows more succulent, but it remains dry. The action of the heart becomes more tremulous, the heart-beat more diffuse, the pulse fuller. The mucous membrane of the mouth is dry, thirst is very great. The subjective manifestations, the headache, the pains in the limbs, the feeling of oppression, decrease, as a rule; however, they may also increase still more. The patient shows excitement which may increase to actual delirium. The temperature remains high. The heat stage may last for several hours, but it is often short and soon passes into the stage of sweating. The turgescient skin, which is greatly filled with blood, gradually becomes moist, at first upon the forehead and in the axillæ, and soon a marked acid perspiration of a peculiar odor covers the entire body. The full pulse becomes softer and more quiet, the tormenting subjective symptoms abate and disappear gradually, respiration becomes deeper and quieter. The urine is dark and usually, upon standing, shows abundant urates. Most patients, at this stage, pass into a quiet sleep from which they awaken, although weak, yet with an undoubted feeling of euphoria. The temperature falls to normal or even below during the sweating stage. It usually lasts longer than the stages of chill and heat and often, when the attack began in the morning, persists during the following night.

The attack is followed by the *afebrile interval*. The temperature is normal, yes, often subnormal, during this period, and the patient feels perfectly well—

in this case he has a "true" apyrexia; but he may suffer also during this period from certain gastric disturbances, loss of appetite, irregular digestion, combined with an indistinct feeling of sickness—then the apyrexia is called "false." It is often false during the first attacks of a first infection and, further, again, upon longer duration of the disease, especially when the normal course is influenced by the administration of drugs.

The typical attacks of fever now alternate regularly with the afebrile periods, hence the name, "intermittent fever." If the attack recurs every day, we speak of quotidian fever, if with an interval of one day, hence every third day, we are dealing with tertian fever; finally, if two days intervene between the attacks, the fever is called quartan, as the attack occurs each time on the fourth day. Special varieties of parasites are peculiar only to the tertian and quartan fevers, not to the quotidian. As was already observed by the ancients, the tertian fevers often pass into quotidian, and, inversely, the quotidians frequently into tertian fevers. Sénac had already pronounced all daily cases to be double tertians, and he denied the existence of the quotidian rhythm entirely. He was actually correct in this contention. It has very often been noted that the various attacks did not conform to one another, in regard to the time of their occurrence, as also in respect to the height of the fever and their duration, but that the first one was always equal to the third and the second one to the fourth. We now know that in this case it is a question of two generations of parasites, one of which reaches sporulation on the first, third, fifth, and seventh days, the second one on the second, fourth, sixth, etc., days.

Sauvage has distinguished, besides the *febres duplices*, also the *febres duplicatæ*, because he observed tertians in which two typical attacks, separated by a short but distinct intermission, occurred every third day.

Similar conditions were also noted in quartan fever and the occurrence of quartana duplex and triplex was recognized. A quartan triplex is clinically a quotidian fever; it may become quartan if the two generations of parasites which sporulate on the second and third days disappear, either spontaneously or due to the administration of quinin. A passing of quartan into tertian fever, and also the reverse, has likewise been observed, and from this a uniformity of the cause of all these varieties has been inferred. Although the observations have been unobjectionable, their explanation was not correct. In these cases a double infection with tertian and quartan parasites had taken place. At the onset only the tertian parasites had caused the attack; these having perished, only the quartan parasites remained, which now produced the attacks corresponding to their type of development.

The ancients described, besides the quotidian, tertian and quartan fevers, also infections with five, six, seven, eight, nine, ten, fourteen and fifteen days, four weeks, three months, and yearly fevers, which were reported to have recurred with typical regularity in the above-mentioned intervals. There is no reason to doubt the correctness of these observations, only the explanations of these types of fever were erroneous. In many cases it was probably a question of infections which had nothing at all in common with malaria, or they were recurrences which, according to the type of development of the parasites, have appeared at regular, but prolonged, intervals. The quintana

which was already described by Hippocrates, and which was observed by Telpius as recurring for eighteen months in a girl with strictest regularity, was declared by Werlhof to be a tertian fever in which always one attack failed to appear. The septan fever, which was also reported by Hippocrates, is explained by Werlhof also, as the decimana, for offsprings of the quartan fever in which always one, or perhaps two, attacks did not take place.

We note, therefore, that even the ancients endeavored to trace all varieties of attacks of fever back to the tertian and quartan types, of which alone well characterized parasites were the cause.

A phenomenon, which has been observed since ancient times, is very remarkable, the so-called anticipation and postponement of the attacks. For instance, Amatus Lusitanus described tertian fevers which regularly antedated three hours, Löw reports quartan fevers in which the attacks regularly occurred ten hours earlier in each succeeding attack. Werlhof believed that it was characteristic of tertian fever to postpone and of quotidians to antedate. It seems that this conduct of the fevers is no longer observed at present as was the case formerly; the postponement might be explained by a retardation of the process of sporulation due to unknown causes, whereas the occurrence of antedatement is only difficult to understand. Manifold infections may possibly play a certain part in this condition.

Regarding the so-called *inverse forms* of the attacks in which heat and perspiration take place before the chill, in these cases it was probably only a question, according to the opinion of Griesinger, of quotidian fevers in which the nocturnal sweat of one attack ceases shortly before the matutinal chill of the following one, so that it should be looked upon only as an incorrect combination of the stages of attacks which rapidly succeed each other.

However, the ancients distinguished still another variety of fever which they considered as especially dangerous. Celsus designates this form as ἡμικριτικόν. He described it as follows: "Tertianarum vero duo genera sunt: alterum eodem modo, quo quartana, et incipiens et desinens; illo tantum interposito discrimine, quod unum diem præstat integrum, tertio redit: alterum longe perniciosius, quod tertio quidem die revertitur, ex octo autem et quadraginta horis fere sex et triginta per accessionem occupat, interdum etiam vel minus vel plus; neque ex toto in remissione desistit, sed tantum levius est. Id genus plerique medici ἡμικριτικόν appellant." The fevers which were treated exhaustively by Torti and which were called by him febres subintrantes have been observed especially frequently in this group. These are fevers in which, in contrast to the usual ones, the attacks persist so long that the new attack already sets in before the first one has ceased. The consequence is that a distinct apyrexia does not develop, but that only a brief abatement of the fever takes place which, accordingly, does not appear clinically as intermittent fever, but as a remittent or even continued one, a phenomenon which Torti designated also by the name of febris communicans or coalterna, and which he considered to be particularly dangerous.

This type of the course of the fever is peculiar to the so-called estivo-autumnal fevers of the Italians, and was then observed especially often in the tropical fevers. The investigations of Koch have shown that all these fevers

are due to one and the same variety of parasites, namely to the small organisms which occur only in ring-form in the blood and which sporulate in the internal organs.

The **clinical course of the tropical fevers** is essentially different from that of the usual intermittent fevers. The prodromes may be absent or they appear as lassitude, disinclination to any sort of activity, sensation of weight in the limbs, nervous unrest, headache, loss of appetite, slight fever, etc.

The chill which is almost never absent in tertian and quartan fevers does not occur in tropical fever. The onset, which almost exclusively takes place toward noon or during the first hours of the afternoon, commences with slight chilliness, soon followed by the hot stage. The patients feel intensely ill, weak, and are prostrated, they complain of severe headache, vertigo, sensations of weight in the limbs, pains in the small of the back; their faces are flushed, the skin is hot, as are also the lips and tongue; the patient is tormented by a violent thirst, the pulse is more or less accelerated, respiration is but little altered. As in the ordinary fevers, however, catarrhs of the respiratory and digestive tracts, coryza, cough, nausea, retching and vomiting, even hematemesis, bloody diarrheas, also hemorrhages from the nose and lungs as well as into the skin, may aggravate the condition. A frequent desire to urinate is present. Albumin is observed but rarely in the urine. The temperature rises slowly but steadily up to 103.6° F., 104° F., 104.4° F., rarely higher. It remains at this height from twenty to twenty-four or thirty-six hours; however, on the following morning, about twelve hours after the onset of the fever, it shows a remission to above 102° F. The patients are often delirious during the fever; in spite of great lassitude, they do not obtain any sleep. This insomnia, associated with a violent headache, causes the attack to be an extremely painful malady. The attack finally terminates with abatement of the disturbances and quite an abrupt fall of temperature. However, perspiration may be absent. Sometimes the temperature does not fall to normal and below but remains at about 100.4° F. After a brief intermission of eight, ten, or twelve hours it again begins to rise, with a new increase of the subjective disturbances, and the new attack follows. The course of the curve of the untreated tropical fever is always that of a tertian fever, as proven by Koch. As determined by Marchiafava and Bignami, the curve of malignant tertian fever and the curve of tropical fever are identical, as are also the two parasites.

The ordinary attacks of malarial fever, as described above, may occur in a very threatening manner under certain conditions, especially in debilitated individuals; nevertheless, they do not lead to death. However, there are varieties in which the pathological symptoms in general, or some of them, are increased to such an extent that the patient may succumb in the second or third attack, although rarely in the first. These are *attacks of the so-called pernicious fever* which may be due to all varieties of parasites, which are, however, preferably caused by the small parasites of the tropical fevers.

The classical descriptions as given by Torti were later scarcely supplemented by any other essential points.

Even with Torti, the question arose why "*varias venenositates suscipere possit fermentum.*" He explains their malignancy by the assumption of a

“major intensio activitatis” the cause of which is unknown: “Indoles solita ignoratur, æque adeo ignoratur intensior insolita.”

The cause of the perniciousness may be ascribed, according to recent investigators, to the intensity of the infection, i. e., to the multitude of the parasites present in the blood. If we consider that Koch found 80 per cent. of all the blood corpuscles of a patient attacked by parasites, that, therefore, four-fifths of the blood corpuscles were rendered more or less incapable of performing their physiological function of absorbing oxygen, it becomes conceivable that a severe danger for the entire organism is associated with such conditions. As, further, the parasites during their growth absorb the hemoglobin of the blood corpuscles and transform it into melanin, this corpus de reliquat, must circulate in enormous quantities in the blood during the process of sporulation and, as a dead mass, give rise to obstructions in a great number of capillaries with all of the ensuing consequences. Besides, however, it is probable that also toxic products of metabolism are present which enter the circulation in the process of sporulation, besides melanin. Golgi noted, during the process of maturation of the parasites, during the disintegration into the different particles, that the balance of the blood corpuscles became suddenly pale. From this observation, he concluded that a toxin probably becomes liberated simultaneously with sporulation and by the same.

We know of quite a number of pathogenic micro-organisms that their virulence may vary under natural as well as under artificial cultural conditions, that they are able to excrete at one time more, at another time less, specific toxin, as, for instance, diphtheria bacilli, or that the substance of their bodies may be more or less toxic. We know comparatively little regarding the cause of this varying virulence. We only know that it may be altered by chemical changes of the nutritive substratum and by thermic influences. It appears probable, therefore, that the malarial parasites, under certain, as yet unknown, circumstances, may attain a peculiar toxicity which then, apart from the number of parasites, gives rise to the production of the pernicious phenomena.

By far the most frequent of these pernicious manifestations are *cerebral and nervous symptoms*.

The headache, during the heat stage, may attain an unusual degree of severity; loud furibund delirium, yes, actual maniacal attacks may develop and terminate either in violent convulsions, especially often in children, or with coma or collapse. Or the patient, after violent headaches and marked vertigo, becomes somnolent, dull and confused, then fully unconscious and, finally, deep coma sets in from which he cannot be aroused. He either succumbs during this condition or he regains consciousness with the occurrence of perspiration, but he remains weak and confused and often retains disturbances of a nervous nature, such as paralyses in some nerve districts, hyperesthesia, paresthesia, hemiplegia, paraplegia. Psychological disturbances are also observed as sequelæ. If a similar attack occur, the patient usually succumbs to it. Sometimes he may present the typical picture of bulbar paralysis. The various forms of lesions of the central organ, running their course under the corresponding clinical pictures, are described as malarial tetany, epilepsy, eclampsia, catalepsy, intermittent bulbar paralysis. The causes of the dis-

turbances in these cases are probably actually the enormous accumulations of the sporulating parasites, as well as of the pigment which has become liberated in great quantities, in the cerebral vessels and in the endothelia, which impart a dark gray violet color to the cortex of the brain.

Very dangerous are the *algid* and *syncopal* [comatose] forms which sets in during the heat stage, with a pulse that becomes quite weak or even disappears, a marble coldness, progressing from the extremities to the trunk, the pale livid skin which is covered with cold perspiration. Respiration is slowed, the voice disappears, but consciousness is undisturbed, gradually the pulse disappears entirely. Raised folds of the ice-cold skin, which is covered with a sticky sweat, remain standing. The patient remains with undisturbed consciousness until the end.

A similar clinical picture, caused by paralysis of the myocardium, due to the above-described effects of the pigment and of the toxin of the parasite, is presented by the so-called syncopal form, in which the patient may be for some time in the condition of *vita minima*, of apparent death, before he succumbs.

If the sympathetic nerve is severely affected, excessive perspiration—intermittens diaphoretica—or numerous cholera stools—intermittens cholERICA—lend their stamp to the clinical picture. Extremely violent gastric pains, as well as uncontrollable vomiting, often of bloody masses, are sometimes prominent—intermittens cardialgica.

Besides, dysenteric, pneumonic, pleuritic, and typhoid forms of malaria have been differentiated, in which the symptoms characteristic of the respective pathological processes set in with the paroxysm and recur, that is exacerbate, rhythmically.

It appears that all these forms are not caused by the malarial process in itself, but they only represent severe complications of the same with other pathogenic agents. More exact bacteriological investigations of such cases have been made only in relatively small numbers. In some cases of so-called *typhoid malaria* a number of true typhoid bacilli were found, besides the malarial parasites; the true typhoid character of the typhoid affection has also been proven by the specific reaction of the blood. If malarial patients with large splenic tumors are affected by enteric fever, the generator of which, as is well known, alters the spleen pathologically, insignificant causes in these patients may lead to *rupture of the spleen*.

The exceedingly dangerous *blackwater fever* occurring in many tropical and subtropical regions will be discussed more minutely later on, in the description of the therapy of malaria.

Besides pernicious forms of malaria, we must also consider the cases of so-called “*masked malaria*.” These are cases which, without presenting typical attacks of fever, are characterized by pathological manifestations of a different kind, which recur in regularly intermitting attacks and disappear after the administration of quinin. Among these are especially manifestations, relating to the regions of the most various sensory and motor nerves and nerves of special sense, intermittent neuralgias in the various branches of the trigeminus, occipital, brachial, intercostal, neuralgias; attacks of sciatica, cephalalgias, hemicranias, spasms of various kinds, anesthesia, amblyopia,

hemeralopia, deafness; further, disturbances of a vaso-motor nature, palpitation of the heart, edema of the skin and of the pharynx, inflammations of the eyes, especially of the cornea, inflammation of all parts of the respiratory and digestive tracts, of the skin, of the organs of generation, etc.; in short, there is scarcely an affection which has not been called masked malaria in malarial districts and during the occurrence of epidemics of malaria. However, the same affection occurs also under conditions in which no possibility of the malarial affection can be proven. But the intermittent character of any affection and its retrogression upon the administration of quinin must not by any means be considered, therefore, as a proof that it is actually due to the malarial process. If an exact examination of the blood were undertaken in all such cases to determine the presence of the malarial parasite, the number of cases of "masked malaria" would probably be reduced to a very small figure.

To return to the attacks, let us now consider the further course of the disease, and we will note that the clinical picture may present very varying forms.

It is often noted that the attacks, even if they are not treated, cease spontaneously in the course of time.

The attacks either retain their rhythm or they lose it. They gradually become milder, the temperature curve more and more assumes the subcontinuous type, the subjective pathological symptoms grow slighter and, finally, they cease entirely. The patient is spontaneously cured. It was known for a long time that tertian and quartan fevers may take such a course; however, that the conditions in tropical fever are the same has not been determined, according to Koch. Naturally, the answer to the question of the cause of these spontaneous recoveries is of great importance. Probably, as in numerous other infectious diseases, antibodies arise in the blood of the patients, injuring the parasites. Some form of auto-disinfection takes place in such cases. All of the parasites may perish during this process—then the patient is cured. However, this is not usually the case, but the parasites react rather to the noxa threatening them in that they form the resistant gametes. At any rate, a number of parasites escape the effects of the antibodies that have been formed and remain capable of life and development.

If the postulated antibodies are again excreted after a lapse of a brief period of time, the parasites which have survived, either schizontes, or, according to the most recent investigations, female gametes, may recommence their cycle of development, the same as in a new infection. Their number will gradually become so large again that their sporulation may produce a new attack; a relapse takes place. These recurrences make their appearance with great regularity particularly in the tropical fevers; especially characteristic is the occurrence of these relapses after the attacks proper have been caused to disappear in the patients by appropriate treatment. They recur every two or three weeks in some individuals, in irregular intervals in other individuals. The intensity of these attacks may be equal to that of the first fevers, but it may also be greater or less. If the attacks are not treated and the process does not show an inclination to spontaneous cure, there develops gradually, the same as in patients who are not cured by the treatment or who suffer permanently from relapses, a condition of *malarial anemia and malarial cachexia*. An increas-

ing condition of weakness becomes manifest in the patients even after several successive attacks, especially if the intensity of the latter grows. A sensation of weight is present in the splenic region; the spleen is enlarged. The early enlargement can frequently be demonstrated by percussion, but after a series of attacks the organ protrudes more or less over the costal arch, as an easily palpable tumor.

The splenic tumor is often absent in patients suffering from tropical fever. Even in fevers of some duration the organ rarely enlarges to the extent that it is easily palpable.

Gradually, the condition of nutrition of the patient suffers; he becomes emaciated, and the complexion at the same time becomes peculiarly pale, gray-yellowish. This picture becomes still more pronounced if the affection has persisted for months or years. The patients are actually pitiable creatures, earth-colored or ashy gray in the face, emaciated and weak, so that they are scarcely able to stand upon their feet. The spleen is enormously swollen, the legs dropsical, the liver enlarged, the abdomen distended by ascites.

If the blood of the patient is examined by means of the Thoma-Zeiss counting apparatus, it will be found that the number of blood corpuscles has materially decreased. Whereas 1 cc. of normal blood contains about five millions of red blood corpuscles, it will be found that their number in patients with waxy yellow color of the skin has fallen to one-half, even to one-third of the above number. The hemoglobin, which can be determined with Gowers's hemoglobinometer or with v. Fleischl's hemometer, accordingly, is materially lower than under normal conditions. If the normal amount of hemoglobin is assumed to be 100, in the case of malarial patients it is only 60 or 50. The lowest amounts of hemoglobin are observed after severe attacks of blackwater fever and in severe cachectic conditions. We find in the blood, apart from the decrease in hemoglobin, numerous pathological conditions of the blood corpuscles, such as are observed in severe anemias, the manifestations of polychromatic degenerations to which we shall refer later on, when discussing the diagnosis of the disease.

Furthermore, a marked increase of the leukocytes can be determined regularly, especially the large mononuclear cells have been found increased by 10 per cent. to 20 per cent., principally during the intermissions. Sometimes a considerable increase of the eosinophile cells is also noted.

Cachectic patients suffer from a variety of disturbances of the respiratory tract (bronchial catarrhs) as well as of the digestive tract (diarrhea, constipation, dyspepsia), of the heart (palpitation of the heart, irregular action of the organ), of the skin (furuncles, edema, partial gangrene), of the nerves and organs of special sense (vague rheumatoid pains, inflammations and necroses of the cornea, optic neuritis, multiple neuritis, myelitis, etc.)

The temperature of the body of a patient suffering from cachexia always presents great irregularities. Sometimes it is a question only of slight attacks of fever, which are subjectively scarcely noticed by the patient; at other times a higher fever occurs without showing, however, the typical stages of the attack.

Dehio, who regularly noted the temperatures of such patients even during the afebrile periods, determined that the temperature of the body is abnormal

also during the intervals: "The average daily temperatures are either abnormally higher or far lower than in the average individual; furthermore, an inclination to abnormally great daily fluctuation is present, as well as sudden and irregular rises and falls in general. Finally, the highest temperatures of the day often occur in the morning and not, as in the healthy, in the afternoon or evening."

Parasites are often absent or they may occur only in the form of gametes in the blood. Death occurs from exhaustion, dropsy, or apoplexy, with the development of amyloid changes in the internal organs.

PATHOLOGICO-ANATOMICAL CHANGES

The acute attacks of so-called benign malarial affections do not terminate in death, whereas those of the pernicious variety do.

The characteristic findings are the accumulations of pigment which can be demonstrated in various organs. Very characteristic changes are found in the brain. The cortical substance, often also the ganglia of the brain, show a gray, grayish-violet to brownish color, which is caused by the pigment present in large masses in the capillaries, either in their endothelia or still in the blood corpuscles containing parasites. It frequently occurs that entire capillary regions are crowded with sporulating parasites each of which contains a central mass of pigment in its interior. The brain is sometimes edematous and plethoric, at other times it may be anemic. It is often noted to be interspersed with small punctiform fleabite-like extravasations of blood. The right heart is dilated, filled with blood. The liver is sometimes enlarged; its appearance is described differently, being sometimes of a slate-gray color, at other times olive-green, again like a decaying cork. The gray tint is due to the pigment which has accumulated in this organ in the same manner as in the brain. The spleen may be normal or it may be soft and appears like a sack filled with a black, pulpy mass of blood, quite in contrast to the appearance of the coarse fibrous splenic tumors found in patients suffering from chronic malaria.

The intestinal tract shows, with preceding diarrheas, catarrhal swelling and reddening of the mucous membrane, in the choleraic form, parts that are of a pinkish-red color the same as in genuine cholera. The kidneys are often hyperemic, permeated by pigment, as is also the bone-marrow which appears decidedly red. In malarial cachexia, we often find atrophy of the kidneys, cirrhosis of the liver, a relaxed atrophic heart, and also, not rarely, amyloid degenerations of the intestine, of the liver, of the spleen, and of the kidneys.

DIAGNOSIS OF MALARIA

In reviewing the history of malaria, we find that formerly the diagnosis of this disease was based almost exclusively upon a number of clinical symptoms, chill with subsequent high temperature followed by sweat, and recurrence of the attacks at certain regular periods. However, experience has taught that often the fevers do not always take this typical course, that sometimes the intermissions may be brief or may be entirely absent. Therefore,

in regions in which malaria existed endemically, each and every febrile condition, no matter whether the fever was intermittent, remittent, or continuous, was finally considered to be malarial. It is obvious, therefore, that a large number of very different pathological processes were diagnosticated and treated as malaria, which had nothing at all in common with malaria. Infectious diseases of the most varied character, especially typhoid fever, tuberculous processes, suppurative processes in the internal organs, especially pyemia, were regarded as malaria.

There was a material progress in the diagnosis, with the introduction of Peruvian bark. It was Torti who maintained most peremptorily that malarial diseases were only such affections as were susceptible to the action of quinin. It is true, even this criterion was not reliable, for many true malarial fevers were not influenced upon insufficient or wrong administration of the quinin.

The positive diagnosis did not become possible until the generators of the disease were discovered by Laveran and the various forms of the generators, their appearance in the blood, their cycle of development had been clearly recognized. To determine in a given case not only the diagnosis of malaria, but also the diagnosis of the forms of the same and of the stage in which the patient happens to be, and, with it, to define the correct time for the effectual or efficacious administration of quinin, requires the microscopical examination of the blood. This is so obvious that properly nothing should be said about it. And yet it is necessary always to emphasize it energetically, as there are still numerous physicians who do not employ this decisive diagnostic method, either because they lack the necessary technical skill, or because the use of the microscope, especially in the tropics, is connected with many difficulties. Regarding the first point, the want of the required technique, this is the case without question with many physicians at present. However, after the methods of examination, as we shall see, have become so very simple, these obstacles will be removed before long. Every physician who establishes himself in the tropics should be required to know and understand the microscopical diagnosis of malaria. The difficulties of the microscopical examination under tropical conditions should by no means be underrated; however, they are not of such a character as to justify the complete foregoing of this aid which is equally valuable in diagnosis as well as in treatment. F. Plehn has prepared a scheme for the treatment of the disease, which is based upon the observation of the temperature and of the duration of the attack. After explaining the same, he continues: "But it is absolutely necessary to have such a scheme as will make us independent of the special result of the blood examination. We may recommend it as much as we please—it is true, I also ascribe a very great practical value to it so long as I am theoretically concerned in hygienic questions of the tropics—upon the whole, it will not play an important rôle in these regions. By far the majority of fevers do not come under medical treatment at all. But to record a regular temperature curve, and to treat the fever accordingly, every layman of average intelligence can and must learn very rapidly when there."

We cannot approve of this standpoint of F. Plehn. If every layman is able, after the simple scheme of Plehn, to treat malaria as well as the scientific

cally trained physician, then medical treatment would be superfluous. What are the results of this unprofessional treatment of malaria? Inconceivable quantities of quinin are swallowed without the prescription of a physician, but the fever persists in many cases, is not cured thereby, and attacks of blackwater fever are then often the consequences of the improper and excessive employment of quinin. It is true, at home as well as in the tropics, a good many cases of fever do not come under medical treatment. This is in part due to the external conditions but partly also to the fact that the patients keep quinin in the house and probably also have a theory according to which they treat every febrile affection. But if the patient comes to consult the physician, it is expected that the physician will now take definite and decisive measures against the disease; this, however, he is able to do only, and all physicians are probably in accord now in this respect, if he has recourse to the microscope and treats the patient according to the result of the positive scientific diagnosis.

Regarding the method of examination, the blood may be examined either *fresh* or on cover-glasses, that is slides, dried in thin layers, and *stained*.

The number of the methods is extremely large. They may all answer the purpose. However, I will confine myself to quoting only those which guarantee a speedy and positive diagnosis.

The first object is to obtain the material for examination, a drop of blood. It is advised to puncture, with a needle or, better, with a lancet, either the carefully cleansed and dried finger-tip or the lobe of the ear or, again, the dorsal part of one of the terminal phalanges (Ruge). To aspirate the blood by means of a sterilized Pravaz syringe directly from the spleen is unnecessary and also not devoid of danger, even if the number of parasites in this blood is larger than that in the peripheral blood.

The drop of blood exuding after the puncture must be utilized as speedily as possible. To see the living malarial parasites, the centre of the drop must be brought into contact with a carefully cleaned cover-glass that is free from grease; the latter is then placed upon a slide. The blood corpuscles are then contained in a thin layer; the blood dries a little at the border, but in the centre it remains unaltered for hours (Laveran). Or a drop that is drawn by means of the platinum loop is mixed with physiological salt solution (von Jaksch punctures through a drop of the latter that is placed upon the finger-tip so that the exuding blood at once mixes with it), or, still better, as the salt solution rapidly renders the parasites motionless, with a drop of human blood serum or human transudate fluid. The parasites are recognized in the preparation, which is examined by means of a microscope and suitable lens, especially easily if they contain pigment granules. They are also conspicuous by their peculiar refraction to light, which imparts a peculiar "porcelain-like" appearance, especially to the quartan parasites. The tertian parasites show very lively ameboid movements, whereas the movements of the quartan parasites take place but slowly and tardily. More difficult of recognition are generally the young forms and the parasites of tropical fever, and especially difficult of detection are the young forms of the latter, the infinitesimal rings. If the latter are present in very large numbers, their determination does not offer any difficulties in the fresh preparation. The diagnosis becomes very difficult, however, if these forms are present only in a few isolated specimens,

as is often the case in tropical, fresh fevers. Changes in form of the red corpuscle, small depressions, fissures, or vacuoles which arise accidentally render the decision still more difficult. Only a well-stained preparation is decisive in such cases. Of importance in the fresh, unstained preparation is also the observation of the flagellated forms which are absent, it is true, in the first fevers. The decision regarding free ovals and spheres causes difficulties. They may be confused with colorless blood corpuscles. The observation of pigment granules does not protect absolutely from confusions, because the leukocytes may have absorbed pigment. However, the differentiation of all these structures is easy, as we shall see, in the stained preparation.

It is essential, in making the preparations ready for staining, to spread the corpuscles in such a manner that they appear intact, with sharply defined contours, deposited side by side, not conglomerated and deformed. This is accomplished best by means of the process proposed by Jancsó and Rosenberger and highly recommended by Ruge. The edge of a cover-glass is passed along the exuded drop of blood, placed at an angle of about 45° upon a cover-glass or an object carrier, which is then moved forward upon the cover-glass forming the base, but which is not the blood covered surface. The edge of the cover-glass is, therefore, not drawn over the spread-out blood, but the blood spreads of its own accord without pressure behind the advancing edge. But even if the blood is spread over the cover-glass, or if a small drop of blood is placed upon a cover-glass, a second one put on top of the other and this drawn off horizontally, a thin uniform layer of unaltered blood corpuscles is obtained. The main point in obtaining good preparations is that the quantity of the drop that adheres to the edge of the cover-glass, that is the size of the drop employed in the drawing off method, be correct.

The specimens are then freed from air and fixed by immersing for five minutes in absolute alcohol, or for one minute in the mixture of alcohol and ether described by Nikiforoff. A few drops of this mixture may also be dropped upon the preparations. As soon as the alcohol-ether has evaporated, the fixation is completed. Naturally, there is no objection to a longer fixation, one or two hours. The preparations will then become more beautiful. An excellent method of fixation, although slightly more inconvenient is that which recently is again greatly recommended with sublimate-alcohol, two parts of concentrated watery corrosive sublimate solution, and one part of absolute alcohol which is applied in a heated condition (60° to 70° C.). Schaudinn drops the cover-glass smeared with blood immediately after the spreading horizontally upon the heated mixture which is contained in a watch-glass, and adds a colder mixture. After a few minutes the cover-glass is placed in 60 per cent. iodine-alcohol, then through alcohol grades up to absolute alcohol, and may now be stained as desired.

If it is intended to keep the preparations, they are preserved unfixed in a vessel in which the air is kept dry by a few pieces of calcium chlorid. Numerous preparations preserved in such a manner were sent to me from the tropics. They often stained well even after years. The absolute dryness prevents the formation of fungi upon the layer of blood, which is so very annoying in the tropics.

A rapid fixation by dry heat may also be employed if the preparations are

intended to be used at once. Then the preparations must be heated, after Ehrlich, for half an hour, or, as I proposed to shorten the process, the cover-glass, held between the fingers, should be drawn three times through a flame.

To stain the preparations, methylene blue, especially the alkaline, has proven to be best of all staining substances. Other staining materials, for instance, carbolthionin described by Nicolle was recommended by Marchoux, a saturated solution of:

Thionin in 60 per cent. alcohol.....	20.0
2 per cent. solution of phenol.....	100.0

and hematin recommended by Thin, do not furnish as clear well-contrasting pictures as does methylene blue. Equally available and durable are: Alkaline methylene blue introduced by me for technical purposes:

100 cc. of a potassium solution 1:10,000.

0.3 cc. concentrated alcoholic solution of methylene blue, borax methylene blue, proposed by Sahli and utilized especially by Manson:

Methylene blue	1 gm. (2)
Borax	2½ gm. (5)
Water	100

or soda methylene blue which is utilized by Zettnow and Nocht especially for the Romanowsky stain to which we shall refer later on, and by Ruge also for simple staining. French authors prefer for the same purpose borrel blue, methylene blue which is left standing for about fourteen days with black silver oxid produced by precipitation of silver nitrate with caustic soda, shaken repeatedly.

Ruge adds to 100 cc. water, 0.2 soda, heats, pours into the solution 0.3 methylene blue, med. pur. Hoechst, cools and filters. The solution has a tinge of violet, the same as the older borax methylene solutions. The reddish-violet shade is caused, as demonstrated by Nocht, in that the so-called "red from methylene blue" has formed. In preparations stained with this solution the red blood corpuscles are stained yellowish-green to bluish-green, the parasites grayish-blue to dark blue, and the nuclei of the leukocytes a brilliant blue. The red corpuscles in the older preparations are very apt to take on a violet tinge. Often blood corpuscles are encountered, the shade of which differs from that of the others which are stained grayish-blue or grayish-green. These "metachromatically" stained blood corpuscles, according to Ehrlich, are older structures that are close upon decay, the discoplasma of which has in part lost the ability of retaining the hemoglobin and which, therefore, no longer takes on the specific normal hemoglobin stain well. This anemic or polychromatophile degeneration becomes especially prominent in staining with a mixture of hematoxylin eosin, in which the changed discs appear violet to bluish red, the normal ones pure red.

Besides so-called "punctated erythrocytes," blood corpuscles with clod-shaped, granular or punctiform deposits in the protoplasm are also often observed, which are seen in anemic conditions of various kinds and described by numerous investigators, first by von Noorden. A. Plehn has found such sparse coarse granules in red blood corpuscles, structures which he designated by the

name of "caryochromatophilic granules," in many individuals in Kamerun who were attacked by malaria or who had only passed some time in this malarial region. He places them in genetic relation to the malarial parasite and assumes "that they might possibly correspond to the latent forms of the malarial parasite," i. e., that they were capable of transforming into parasites. Lazarus considers the significance of these structures, which are frequently found in progressive pernicious anemia, as not fully explained as yet, but he inclines to the belief that they are products of the nuclear degeneration within the blood disc, which is favored by their occurrence in embryonal cells. They have certainly nothing in common with the malarial parasite.

The older the solutions, the more intensely and rapidly do they stain. It is necessary, therefore, to avoid overstaining of the blood corpuscles, to dilute sufficiently with water. Overstained preparations must be decolorized to facilitate the recognition of the parasites. To accomplish this, the preparations are either washed in a weak solution of acetic acid 1:1,000 to 1:2,000 or, according to the proposition of Kossel, in a 2 per cent. methylal solution. I found a mixture serviceable which was prepared as follows:

Tannin, 1:1,000, 4 parts; methylene blue acetate ($\frac{1}{2}$ per cent. methylene blue, $\frac{1}{4}$ per cent. acetic acid) one part.

Preparations stained by a brief immersion in an alkaline solution of methylene blue are washed in water and then for a few seconds stirred in the mixture. They then turn suddenly red. This change to red is due to the action of the tannin. They should then be rapidly washed with water and examined. The intensely blue stained plasmodia are very easily recognizable in the blood corpuscles which have stained red. If the tinction has been accomplished with a red tinged older borax methylene blue solution, the chromatin appears, especially in the young parasites and in the preparations of the tropical fevers, stained a brilliant red, the same as in the Romanowsky stain which will be discussed presently. In this manner the parasites may be easily demonstrated even in old preparations.

The finding of the large tertian and quartan parasites in preparations stained in the above manner does not present any difficulties whatever to those who are at all experienced. Only the search for the small and medium-sized tropical rings may, especially when they are not very numerous, require a more prolonged and thorough use of the microscope.

The finding of isolated small forms is facilitated for those that are less expert by the employment of *double stains*. Eosin and methylene blue are almost exclusively used for this purpose. Some authors prefer to first stain the preparation red by a brief immersion in 1 per cent. eosin solution, followed by the blue stain; others are more in favor of a mixture of both stains, performing the tinction in one process. Numerous mixtures have been given for this purpose. Good results are furnished by mixtures of Chenzinsky and of Plehn:

Forty cc. (Chenzinsky), or 60 cc. (Plehn) watery methylene blue solution; 20 cc. $\frac{1}{2}$ per cent. eosin solution in 70 per cent. (Plehn 75 per cent.) alcohol; 40 cc. distilled water.

Plehn adds 12 drops of a 20 per cent. caustic potash solution. Time of staining with Chenzinsky stain six to twenty-four hours at the temperature

of the blood, with Plehn one to five minutes. Washing with water. The blood corpuscles are stained pink, the plasmodia light blue, which therefore stand out prominently; the nuclei of the leukocytes are dark blue, the granulations of the eosinophile cells red.

However, the finest and most characteristic pictures are furnished, beyond dispute, by the staining method of Romanowsky which, as we have seen, has been fundamental for the more minute knowledge of the development of the malarial parasites, as it disclosed the chromative substance of the nucleus of the parasite. Acting upon the knowledge that the nuclei of the majority of all cells incline to neutral and basic colors, Romanowsky endeavored to find a basic methylene blue and acid basic eosin. When mixing filtered water in solutions in both substances he observed the occurrence of a moment in which, with a beginning excess of eosin, a precipitate arose which was insoluble in the mixture and which imparted to the latter a tinge of violet. He found that the precipitate was distinct in the proportion of one part of concentrated methylene blue solution and two parts of 1 per cent. watery eosin-solution. Romanowsky writes: "The mixture has a very superior power of staining at this moment; the nuclei stain especially well, while the colors by no means lose their peculiar selective quality; however, besides the stains employed, a third very peculiar color forms in the mixture, which possesses the greatest affinity for the nuclei, or to express it better, to their chromative network." Romanowsky has recognized almost all factors which are important in staining, more diluted solutions of methylene blue furnish less precipitates, but they require longer time for staining, twenty-four hours instead of one-half to three hours; old mouldy methylene blue solutions stain best; not every methylene blue is suitable for staining. However, in spite of the most exact statements of the excellent results, the stain did not become popular, at least in Germany. Not until Ziemann and, above all, Koch had recognized its great significance did it become the object of exhaustive studies. The most appropriate colors were recognized to be methylene blue, med. Höchst and the bromeosin B. A. extra, also of Höchst.

Nocht found that a structure which forms in the old solutions the "red of methylene blue," is essential to the development of the chromatin stains, that the staining power of the solutions can be materially increased by the addition of Unna's polychrome methylene blue which contains large quantities of this substance and by the application of heated alkaline solutions during which the same develops in large quantities.

Reuter prepared the substance which was eliminated from the alkaline methylene blue by eosin—alkaline methylene blue eosin—and found that the alcoholic solution of the same, diluting with water in the proportion of 1:20 furnished a fine stain.

Based upon the exhaustive chemical studies of Bernthsen on the product of the decomposition of methylene blue, Michaelis determined that neither methylene violet nor methylene red, but only methylene azure, which is formed by oxidation of methylene blue and which contains the sulphurous group (SO_2) is the substance which causes the chromatin stain.

Giemsa finally succeeded in manufacturing pure "*methylene azure*" so that at least a simple preparation is at our disposal, which, mixed with the

proper quantity of eosin, always guarantees speedily and with certainty, beautiful preparations without precipitate. Upon exhaustive experiments with mixtures of this coloring substance with methylene blue it was found that mixtures of equal parts of blue and azure furnished very serviceable stains in so far as the parasites which were stained blue presented the pure blue shade which is very advantageous for differentiation and which is obtained upon staining with pure methylene blue eosin, whereas, on the other hand, azure was still present in sufficient quantities to bring out the chromatin stain distinctly; the precipitate arising during this experiment is easily washed out with water.

The firm of Grüber and Hollborn, Leipzig, furnishes the pure methylene azure chlorhydrate under the name of azure I (pure) and the coloring substance most suitable for the staining of blood, methylene azure chlorhydrate pure + methylene blue med. Höchst & Co., under the name azure II, for staining of blood. We then prepare:

1. A 0.8 per mill solution of azure II, and
2. A 0.5 per mill watery solution of eosin Höchst extra soluble in water, in that 5 cc. of a 1 per cent. eosin solution is diluted in 1 liter of water.

To obtain the mixture of colors 10 cc. of eosin solution are taken to which is added 1 cc. of the azure solution; this is shaken and then poured upon the alcohol hardened preparations which are placed in coloring blocks with the smeared surface downward, the staining is finished in fifteen to thirty minutes. Wash with a strong current of water and examine the preparations in water. If they are slightly overstained after prolonged staining, they should be run through strong 96 per cent. alcohol or through methylene blue acetate ($\frac{1}{2}$ per cent. of methylene blue, $\frac{1}{4}$ per cent. acetic acid), then washed with water, dried and examined with oil.

If no methylene azure is available it is best to stain, according to Nocht in diluting 2 to 3 drops of a 1 per cent. eosin solution with 1 to 2 cc. of water, adding in drops of a soda ($\frac{1}{2}$ per cent.)—methylene blue (1 per cent.)—solution which keeps for several days at 50° to 60° until the mixture is so dark that the original admixture of eosin can no longer, or only with difficulty, be recognized through the color. The preparation should float for five to ten minutes upon this mixture.

It is extremely easy to recognize the parasites, in preparations stained according to Romanowsky, which are stained a beautiful blue, with their brilliantly red chromatin nucleus, in the blood corpuscles which are stained pink, so that even quite isolated young tropical parasites cannot be overlooked.

But, besides, the chromatin stain is of decisive importance also *differentiologically*. There exist no normal or pathologic morphotic constituents of the blood which could be confused, if only slight attention is paid, with chromatin-stained malarial parasites. At most the blood plates might give rise to such a mistake. They are stained intensely violet red and may eventually be deposited upon a blood corpuscle, so that upon superficial observation they may resemble parasites. However, they do not possess the blue body of a parasite and, besides, their edges are not round but serrated. If nucleated red blood corpuscles are present in the preparation, their nuclei appear stained an intense red-violet, the same as the nuclei of the leukocytes. The mononuclear

leukocytes, the protoplasm of which shows a similar blue stain to that of the parasites, cannot give rise to mistakes nor to confusion with eventual free forms of the parasite, as their large, round, deeply violet nuclei characterize them sufficiently.

The *diagnosis of the tertian fever* is materially facilitated by the condition of blood corpuscles which harbor half-grown or adult parasites. They are enlarged. Their diameter is one-half to three times as great as that of a normal blood corpuscle. Upon weak staining after Romanowsky they are stained a pale pink, upon more intense staining, however (Maurer has distinguished four grades), they show an extraordinarily characteristic red dotting which Ruge has compared to the granulations of eosinophile cells. This dotting of the blood corpuscles occurs in that a red coloring substance precipitates upon the blood corpuscle, due to the alteration of the entire mass of the blood corpuscle, which is brought about by the vital activity of the parasite. Schüffner was the first to call attention to this dotting. After he had stained blood preparations from which he had previously eliminated the hemoglobin, with hematoxylin, he noted small bluish dots upon the affected blood corpuscle. Ruge and Maurer found this dotting during their experiments with the Romanowsky stain.

Maurer believes, regarding the nature of the dots, that the latter have nothing in common with the rest of the nucleus of the blood corpuscle, but that they are nothing else but the changed stroma of the blood disk. "They appear from the onset, uniformly distributed through the entire blood disks as very fine dots, they grow with the enlargement of the blood corpuscles, namely with that of the parasite, not in number, but only in bulk."

Schaudinn believes the occurrence of the dotting to be as follows:

"The stroma of the red blood corpuscles is of a uniformly fine alveolar structure; the substance of the nucleus which, before the differentiation of the blood corpuscle, represented a morphologically well defined central cell nucleus, during the differentiation and condensation of the protoplasm has become distributed over the entire erythrocyte and intimately combined or mixed with the plasma (possibly it may in part also have been expelled). A remnant of the original nucleus which can be demonstrated by staining, has remained occasionally in the centre only. The young tertian parasite withdraws from the affected blood corpuscles at first the fluid constituents which can be most easily resolved and which are replaced by absorption of fluid (in consequence of this swelling, hypertrophy) from the blood plasma. However, the easily digestible constituents of the red corpuscles are not the nuclear, but the plasmatic parts; as we know that in the digestion of all cells that are more closely investigated, the chromatic substance always exists longest. In the resorption of the stroma of the erythrocytes, therefore, some form of precipitation of the nuclear constituents contained in the same is brought about. The plasma surrounding it is digested and its place occupied by fluid from without; therefore, the blood corpuscle appears more coarsely vacuolated and paler, each vacuole contains a dot, and upon further resorption the eliminated or remaining nuclear substance accumulates in continuously increasing masses."

Intensely blackish-red dotting of the blood corpuscles harboring tertian parasites is obtained very rapidly, as I have found, if the preparations are

stained by emulsion in an alkaline methylene blue solution containing plenty of methylene blue azure and then stirring them in a 1 per cent. tannin solution until the preparation that was stained blue has become red. Blood corpuscles with very young parasites do not as yet show any dotting. However, as in tertian fevers, even if mostly young forms are present immediately after the attack, always some older parasites are found, and, as a dotting has never been observed as yet in the quartan and tropical fevers, this can be utilized excellently in the differential diagnosis as a sure pathognomonic characteristic of tertian fever.

Besides the dotting of the host cell, some morphological factors must be considered in the differential diagnosis. Thus, especially characteristic of quartan fever is a form which has frequently been observed in parasites that are about six hours old: The parasite extends as a broad ribbon across the blood corpuscle so that a segment of the latter can be recognized on either side of the band.

The sporulation forms of both parasites must be considered especially. In the tertian parasite there are 12 to 24, on an average 16, chromatin-containing segments grouped irregularly around the pigment conglomerated into one place. At most only a very narrow pale ring of the enlarged blood corpuscle can be noted. The segments in the quartan parasites, 8 to 14 in number, are arranged mostly regularly, daisy-like around the pigment conglomerated in the centre.

The diagnosis of tropical malarial fever during the first attacks is based upon the exclusive demonstration of the smallest, medium sized or larger rings, in the absence of more bulky pigmented parasites, in fevers that have persisted for some time and in recurrences upon the demonstration of crescents.

Sporulation forms are only exceptionally present in the peripheral blood. If accidentally such a form is found, it resembles that of the tertian parasite, only it is smaller, as its size does not exceed that of the normal blood corpuscle; the number of the segments is also small.

Maurer has quite recently called attention to a new, important tinctorial characteristic of tropical malarial fever, or as expressed by him of *pernicious malaria*, to the "*perniciosa macula*," as he calls them, of the red blood corpuscles. By a very pronounced staining after Romanowsky, which he was able to accomplish by the mixture of 10 drops of a 1 per cent. methylene blue solution, matured after the addition of 1 per cent. of caustic potash, during four to six weeks at a tropical temperature (in 25 cc. water) with 15 drops (in 25 cc. water) of a 1 per cent. eosin solution, he succeeded in bringing out in the blood corpuscles that were affected by the greater ring forms of the parasite, a number of intensely red maculæ which upon closer inspection appeared as dots, finest of small rings, loops or stripes. These maculæ were always present, and they were more sparse or more numerous in keeping with the smaller or larger size of the parasite. A closer study of these peculiar maculæ led Maurer to the statement that in this case it was a question of changes, that is, losses, of substance at the surface of the erythrocytes, due to attacks of the parasite, undertaken by the latter in adhering to its carrier to procure nourishment. Maurer particularly emphasizes that the occurrence

of the maculæ on the host cell of the pernicious parasite which, however, can only be produced by the strongest degree of the Romanowsky stain which he designates as the "fifth," is an *absolutely regular and unambiguous phenomenon, and that we are enabled by its presence alone to establish at once a diagnosis of "pernicious malaria."*

Accordingly, the demonstration of the uniform dotting of the host cell would at once permit of the diagnosis, tertian fever; the proof of irregular pernicious maculæ, at once, the diagnosis of tropical malarial fever; in the absence of both phenomena, the diagnosis quartan malarial fever.

Determination of the stage of the disease to which the patient has progressed does not, upon the whole, offer any difficulties in view of the fact that attacks and processes of sporulation coincide. According to the scheme, sporulation forms will be found in tertian and quartan fevers shortly before and during the attack, after the latter has passed, small non-pigmented endoglobular forms and, subsequently, according to the duration of the apyrexia, larger and more pigmented forms; in tropical malarial fever the large rings will be noted during the end of the attack and during the intermission, the small rings at the height of the fever.

However, the explanation of the situation as found is very frequently rendered difficult by various factors.

The process of *schizogonia*, which embraces the loosening of the chromatin of the nucleus, the arrangement of the same in an equatorial plate, the splitting of the plate, the constriction of the segments into daughter nuclei, the division of the plasma, the accumulation of the pigment in larger masses, the development of the merozoites and the liberation of the latter, requires about twelve hours in the tertian parasites and twenty-four hours in the quartan parasites. However, this process does not begin simultaneously at a certain period of time in the numerous sporulating parasites, but at various moments, which may be hours apart.

For this reason, the attack is always more or less protracted. It is possible, therefore, to encounter, side by side, mature sporulation forms, adult forms that do not yet sporulate distinctly, and young endoglobular merozoites, yes, even larger rings with distinct nutritive vacuoles.

Secondly, there are probably always some parasites which do not attain sporulation and which gradually perish. Thus, the presence of full-grown parasites is explained at a time after the attack during which only young forms should be expected. However, these decaying forms, destined to destruction, are easily recognizable as such by means of the Romanowsky stain. They are stained pale blue, the chromatin, the same as in the forms destroyed by quinin, is indicated as a finely granular, reddish mass, or it may not be stained at all.

Especially confusing, and upon superficial observation, difficult of recognition is the picture if the formation of the gametes intended for exogenous development of the anopheles has already begun or is in full activity. The gametes of the hemosporidia occur when the body of the host commences to react to the parasites, they usher in the quiescent stage of the asexual propagation.

Usually they do not occur until the patient has passed through several

attacks, sometimes, however, they may appear earlier. Schaudinn has determined them even after the first attack, in a tertian fever.

The development of the gamete from the merozoites to the finished, mature organism, according to the exhaustive investigations of Schaudinn, regarding the development of the gamete of tertian fever, lasts twice as long as the development of the merozoites into the sporulation form. It would be possible, therefore, that young gametes the size of half-grown parasites, might be present in the microscopical picture, synchronously with segmentation forms, full-grown gametes in all stages of the disease.

However, the most recent investigations of Ruge are not in accord with the statements of Schaudinn. Ruge maintains that the greater part of the gametes formed until then is destroyed by every attack of fever, and that the new generation of gametes develops during apyrexia exactly the same as the new generation of schizontes, i. e., the schizontes as well as the gametes in the tertian parasite require forty-eight hours to develop. That this is actually so, he claims to be able to recognize from the almost entire absence of full-grown gametes during apyrexia and from their frequent occurrence at the onset of the fever. This important question certainly requires further study.

It is not so very difficult to differentiate the gametes from the schizontes. The characteristic signs are the following: The sexual forms are without the so-called nutritive vacuole; young gametes, therefore, never appear in ring form. The plasma is denser than in the schizontes, it stains much more intensely in the female, the macrogametes, than in the schizontes, whereas it stains pale in the male gametes, the microgametes.

The gametes are *much richer in pigment*, containing twice as much as the schizontes, the individual pigment parts are rod-like and almost always two to three times as large as in the schizontes. The length of the pigment parts in the schizontes fluctuates between immeasurable shortness and about $\frac{1}{2} \mu$, in the full-grown gametes between $\frac{1}{2}$ and 1μ . The pigment, as Schaudinn has found, is doubly refractive. With Nicol's prisms it is possible to observe in the youngest microgametocytes, even before a distinct pigment granule is shown in the plasma, a double refraction at the boundaries of the nucleus toward the protoplasm, caused by the occurrence of smallest particles of pigment. In the full-grown parasites the plentiful coarse pigment is distributed over the entire plasma, and is especially conspicuous upon the pale plasma of the male parasites; it shows a lively molecular movement in the living parasite.

The cell nucleus is *almost always situated peripherally*. It measures in the microgametes, if spherical 4 to 5 μ , if stretched longitudinally, 7 to 8 μ , with a breadth of 2 μ ; the nucleus, which in the full-grown free forms often is spindle-shaped or band-shaped, in the microgametes of the latter even attains a length of 10 μ with 3 to 4 μ breadth. The nucleus of the full-grown schizontes measures at most 3 μ . The nucleus of the gametes is rich in nuclear fluid, suspended in the junctions of a coarse, colorless and but slightly stainable network; distributed more or less uniformly, are chromatin lumps of various shapes, in the male gametes in the form of thick, plump clumps, threads, cords, and trabeculæ.

The lively ameboid motility of the schizontes is absent in the gametes.

The mature gametes are extraglobular and free in the plasma, their shape is generally round, rounded polygonal, or short oval, rarely ellipsoid. They are always larger than the full-grown schizontes, their diameter is frequently 12 to 16 μ , against 10 μ of the schizontes. It seems that the male gametes remain slightly smaller than the female.

They can at once be distinguished from colorless blood corpuscles, in the first place, by the coarse pigment distributed over their entire body, and secondly, by the absence of a large easily stainable nucleus.

Ruge, to distinguish gametes from schizontes, emphasizes especially the position and the manner of growth of the chromatin. These tertian parasites in which the chromatin is situated within a plasma ring, and at that within an oval or bean-shaped chromatic zone and not in the plasma proper, must be considered as gametes. The chromatin, which appears as a compact granule or rod, angularly loosens upon growing, and, finally, disintegrates into a large number of granules fine as dust, but it always remains whole. The plasma grows in different ways, either the original tertian ring grows as such or the plasma grows from the external border of the crescent-shaped thickening of the ring and then assumes the form of a square or rectangle—the female gamete preferably grows in this form, or, again, it grows from both halves of the ring. It is very difficult in the latter case to recognize the gametes as such (see Plate).

The young gametes of tropical malarial fever, which Stephens and Christophers have found in the blood of negro children in West Africa, were about one-third the size of a red blood corpuscle, stained uniformly in the periphery, already containing some pigment granules, but having no chromatin ring. The full-grown gametes did not occur in the well-known crescent shape but they resembled those of the quartan parasites. The full-grown male gamete was distinguished by a brownish pigment accumulated in the centre or extending through this in the shape of a broad ribbon, and by twelve to twenty triangular bodies situated at its periphery, and markedly stained chromosomes; the full-grown female gamete could be recognized by its black pigment distributed irregularly over the entire parasite and by at most one or two more markedly stained particles.

Maurer gives an entirely different description of the development of the gametes of malarial fever. He studied them in preparations stained in the fifth degree of Romanowsky's method. He determined, at first, that the blood corpuscles harboring gametes do not present any pernicious maculæ. The young gamete represents a circular disk of medium-sized ring-shape, in which the nucleus and the protoplasm have a uniformly broad band enclosing the central colorless nutritive fluid. Upon intense staining a thick red ring is noted surrounding the parasite in a wall-like manner, and separated from its surroundings. Maurer was able to demonstrate this ring in all stages of the crescent growth. This red ring is the very pigmented substance of the corpuscle which the gamete has "sucked out" and which stains intensely red in the Romanowsky stain. The vacuole disappears later. The considerably enlarged, greatly broken up nucleus is no longer differentiated as conspicuously as before in the protoplasm; besides, coarsely granular pigment appears now. The gamete subsequently loses its ring form and the female gametes become

crescent-shaped, the male ones are shorter and broader, bean or kidney-shaped, and the nucleus in the latter is larger. Both sexes are always surrounded with a more or less thick cover, the remnant of the host cell which is stained intensely red and which Maurer calls "capsule of the crescent."

As to the numerical proportion of male to female gametes, Stephens and Christophers found in tropical malaria the number of males equally as large or larger than that of the females, on an average 53 to 33, whereas Ruge found it extraordinarily fluctuating in tertian fever between 1:1 and 1:50. It may also be mentioned that Schaudinn noted a gradual disappearance, after the attack, of the microgametocytes, the male gametes, of tertian fever, whereas the females persisted. He found only macrogametes, three to six weeks after the attack if parasites were present at all in the peripheral blood.

According to the above brief description, it will not be difficult, with some practice, to distinguish in well-stained preparations the gametes from the schizontes, to decide correctly in regard to the forms essential to the diagnosis and to diagnosticate correctly the stage in which the patient happens to be from the conditions found. The diagnosis becomes more difficult, however, if a tertiana duplex, that is, a quartan duplex, or even triplex, are present. In such cases we may find parasites of all sizes, ring forms, half-grown, full-grown and sporulation forms, side by side. The picture becomes especially complicated if we are dealing with mixed infections of tertian and quartan fevers, respectively, of tertian, quartan fever, and tropical malaria. The young ring forms of the former cannot be distinguished from the large rings of tropical malaria. The diagnosis only becomes positive in such cases by the proof of typical sporulation forms of tertian and quartan fevers as well as of the characteristic crescents of tropical malaria, on the one hand, and of parasites in dotted blood corpuscles (tertiana), of Maurer's maculæ in blood corpuscles, with large rings, and of small distinctly circular rings (tropical) on the other hand.

The absence of spheres in tertian and quartan fevers and of crescents in tropical malaria shows that it is a question of a recent infection existing for only a short time, a so-called *first fever*.

From the above, it will be seen that the diagnosis of the manner of infection also of the stage of the disease may probably be made in a great number of cases by a single microscopical examination of the blood preparation. However, many cases exist in which it is possible only by repeated microscopical examination combined with careful clinical observation of the patient, to arrive at the diagnosis. It is necessary, therefore, to lay special stress, besides, upon the microscopical examination, and particularly upon careful temperature records of the patient. If these measurements are meant to furnish a serviceable temperature curve they must be made at least every four hours. Compared with the temperature curve, the microscopical findings will speedily lead to a correct diagnosis.

In order to make a rapid diagnosis of malaria, especially of the latent form, Italian authors have endeavored to find a sero-diagnostic method. Panichi and Lo Monaco have found that the blood of healthy individuals is agglutinated by the blood serum of malarial patients. The future will show whether or not the agglutination test can be utilized in establishing the diagnosis.

THE TREATMENT OF MALARIA

The sovereign remedy in the treatment of malaria, as is well known, is *quinin*. Since 1638, when the wife of the Viceroy of Peru, Countess Cinchon, at Lima, was cured of an obstinate intermittent fever by Peruvian bark, which was recommended to her by the Corregidor of Loxa, J. Lopez de Canizares, which had been found to be efficacious in his own district, and after the physician, Juan del Vego, had imported, in 1640, a large quantity of the bark into Europe, the triumphal march of this wonderful remedy through the world began. The "*pulvis comitissæ*" was employed everywhere. It is true the new remedy soon aroused animated discussions as, especially, the adherents of Galen believed their entire system threatened by the new arcanum which removed the fever without causing an evacuation of the disordered fluids. The brilliant successes, which were reported by Sydenham and Francesco Torti decided the victory of Peruvian bark along the entire line. Torti condemned those physicians who wasted precious time on other doubtful preparations, especially in the pernicious tertian fevers, which were masterfully described by him. He compared the bark with the rope that is thrown out to a person drowning in a vortex. "*Si quispiam natandi nescius mergatur in vasto gurgite, nec illi quidquam circumprostet, quod possitprehendere, ut emergat, is profecto, licet semel aut bis conatu suo naturali, et vi subeuntis aquæ, sursum trusus efferatur nonnihil, cito tamen et certo soffocabitur, ni illi baculus vel quid simile porrigatur ab adjutrice manu. In gurgite mergitur Aeger ex Perniciosa Febre algidus factus, et sine pulsu, utut paululum relevari semel ac iterum videatur. Lignum extrahens e gurgite est Peruvianus Cortex, rite porrectus. Manus adjutrix est manus Medici, illum methodice ac opportune porrigentis.*" He distinctly emphasizes that the quinin acts as an antidote upon the cause of the fever, upon the ferment, without causing any evacuation whatever of an injurious material. With Sydenham, he rejects all additions to Peruvian bark, except those that are necessary to the administration of the drug: "*Qui aliquid Cortici adjiciunt, præter vehiculum eidem in ventriculum transmittendo necessarium, aut ex ignorantia peccant, ut mihi videtur, aut dolo malo, a quo vir probus ex animo abhorrebit.*" Therefore, he recommends the powdered bark alone in wine. But he lays the utmost stress upon the correct method of administration.

He recommends, in the ordinary fevers, the benign tertian fevers, to give two drachms (7.2 gm.), and to administer it sufficiently early before the attack that is to be prevented, i. e., either at the beginning or toward the end of the previous one, then, after one or two days, on two days in succession one drachm, and subsequently, to prevent a recurrence, for eight days every day early in the morning $\frac{1}{2}$ drachm (1.8 gm.), thereafter, in about fifteen days, for six days, in the morning daily one scruple (1.2 gm.), the latter administration to be repeated several times if necessary. He emphasizes particularly the amount of the first dose to be taken at once, 2 drachms (7.2 gm.). For, he says, six scruples (7.2 gm.), taken on six succeeding days, are by no means equal in efficacy to two drachms (7.2 gm.) taken at once, although the weight of the bark administered is the same in both cases. He strikingly compares the effect of the quinin upon the fever with the action of water upon fire.

Whereas a wood fire can be easily extinguished with a pound of water if it is poured over the fire at once, two pounds will not be sufficient to accomplish this if it be dropped into the fire drop after drop and at long intervals. To treat the severe pernicious fevers, in which it is of importance to supply the paths which the ferment of the future attacks is bound to follow as rapidly as possible with the Peruvian bark, so that the fresh attack which generally leads to death be prevented or at least be rendered less severe, he advised six drachms to one ounce to abort the attack and the same quantity to prevent the recurrences. If only a brief period of time should intervene before the expected fatal attack, it is necessary to administer half an ounce at one time and after each six to eight hours following 1 drachm, but in such a manner that the last drachm is given at least twelve hours previous to the expected attack for, taken only a few hours before the attack, quinin is no longer capable of influencing the latter. For the after treatment of perniciosa, Torti recommends 1 drachm daily for three days, followed by $\frac{1}{2}$ a drachm twice a day for three further days. This means 6 drachms before the attack and 6 drachms afterwards. To prevent recurrences he advises taking half an ounce after an intermission of six days in doses of half a drachm each so that a total amount of 2 ounces within three weeks and one week's intermission, may prevent a perniciosa which otherwise would have at once overpowered the individual, whereas, on the contrary, with 4 or 5 ounces administered by an unskilled method, "*enervi methodo exhibitis*," a benign fever could scarcely be driven out, "*vix pellatur benigna*." Should a recurrence take place after the lapse of some time a mild treatment is sufficient, eventually after venesection, one-half drachm (1.8 gm.) or 1 scruple (1.2 m.) daily in the morning for twelve days, to prevent any recurrence of the fever.

The question of the practical treatment of malarial fever was really definitely solved by the classical explanations of Torti regarding the mode of action as well as the method of administration of Peruvian bark. The manufacture of the most active substance of Peruvian bark, quinin, by Pelletier and Caventou, in 1820, and the production of quinin salts were only able to simplify and produce a more certain cure. It is true, the starting-point of Torti's theory, the specific action of Peruvian bark upon the course of the fever, was entirely lost sight of in the course of time. His doctrine was replaced by the theory which attained general acknowledgment that intermittent fevers were due to abnormalities of the nervous system and primarily to a disturbance of the ganglia of the abdominal nervous system.

Quinin and its alkaloids were administered, therefore, as the most prominent nervines, in order to eliminate these quantitatively and qualitatively abnormal activities of the nerves. Sobernheim, in his *Text-Book of Practical Materia Medica* (Berlin, 1840), writes as follows regarding the indications for the use of quinin, rendering the then prevailing views: "1. Intermittent fever. Quinin has gained a permanent reputation as well as the name of a specific remedy in this disease and, immaterial how many surrogates have been recommended in its place, owing to the high price, from alkornoko, mahogany wood, common yellow wall lichen, barks of chestnut and willows, down to spiderweb and the sawdust of *autenrieth*, none have been able to replace it. That quinin heals intermittent disease principally owing to its alkaloidal con-

stitutents, has already been mentioned (see mode of action) and for this reason it is probable that quinin salts are at present most generally preferred (especially the medicinal quinin sulphate). It may be added here that the fever itself, considered as a *conamen naturæ medicatricis* upon the nervous abnormality, is entirely outside of the sphere of these healing actions, which is shown sufficiently by the fact that, on the other hand, these febrile reactions are rendered more intense by quinin in quotidian intermittents which have a tendency to inflammations, whereas, on the other hand, in those cases in which, owing to some circumstances, these solitary efforts of nature cannot be displayed sufficiently or even may be prevented entirely and in which, therefore, the nervous affection alone remains prevalent, as in the so-called malignant or pernicious (amaurotic, apoplectic, soporous, plethargic, cardialgic, occurring with cholera nostras and other dangerous symptoms) and masked intermittent fevers, the cure is accomplished the more surely and the more speedily. Finally, regarding the different varieties of intermittent fever, it must be stated, as mentioned, that the quotidian fever and the tertian fever which occurs with an inflammatory character, especially in youthful, robust, burly individuals—for the reason stated above—and the quartan fever—owing to the morbid retentions, stagnations and swellings in the large assimilative abdominal organs and especially in the liver and spleen, which are mostly at the bottom of this variety, finally—the gastric form with impurities in the first ducts, indicate quinin after the previous employment of antiphlogistic loosening and mildly purgative methods, whereas the pure tertian and the malignant and pernicious intermittents and also the masked forms require it at once.”

The method of employment of quinin and its salts has not been influenced to any extent by theoretical considerations of its method of action. Sobernheim makes the following statements regarding the doses: “Quinin sulphate should be given every two hours in larger doses in such pernicious forms of intermittent fever, of 2 to 4 to 6 grains (0.12 to 0.24 to 0.36 gm.) in threatening cases even 1 scruple— $3\frac{1}{2}$ (1.2 to 1.8 gm.).”

To prevent relapses, he writes as follows: “After the intermittent fever (due to the specific alteration of the abdominal nervous system) has disappeared, it will be well to prescribe Peruvian bark for some time following, in that the malady otherwise is very apt to return. The total dose of quinin to be administered in quotidian and tertian fevers is, according to Gittermann’s results, compiled from several thousands of observations, 12 to 16 gr. (0.72 to 0.96 gm.), but in quartan fever 20 gr. (1.2 gm.).”

Primarily, the use of the drug by the mouth is valuable, but in case of great tendency to vomit it may be given by the rectum or also endermatically, by applying the salt upon an area of the skin from which the epidermis has been removed, or, finally, by a dry rubbing into the skin.

Twenty-five years later Griesinger, in his excellent monograph on malarial fevers, summed up his experiences as follows: “After an experience of several hundred cases, I can but agree in every respect with the mode of giving only one or a few relatively large doses, a method which had already been observed to a great extent in the very first experiments with quinin (1820, Doubel, Chomel), and determined later by some of the most experienced

physicians (Maillot, *Traité des fièvres intermittentes*, Paris, 1836, page 362), and which has since been so universally confirmed as valuable, according to the manner stated by Pfeufer. A dose of 10, in new cases only 8, in more persistent and severe cases of 12 even 15 gr. in one dose, given as a powder or in a few pills, as a rule prevents the attacks in such a manner that at most only the next attack takes place but briefly, and frequently it is postponed, but very often even this fails to appear and then the patient remains without fever for some time. In children between four and six years of age, I administer from 3 to 5 grains, to those between ten and fourteen years, 6 to 7 grains. Recently I always prescribed for one of the days following the cessation of the attacks, another dose of 10 grains; if the patient remained under my observation I repeated this in the same dose in a few days. Even inveterate quartan fevers are occasionally entirely cured by a single dose, although generally they require several repetitions of the same. However, recurrences are not quite as rare in this country as is claimed by some; I have stated the proportion above (Griesinger has observed in 414 cases, $208 = 50$ per cent. recurrences; of these $113 = 54$ per cent. recurred a second time, and of these $50 = 40$ per cent. a third time; of the latter 50, $17 = 34$ per cent. had a third relapse). If such recurrences take place frequently I order quinin to be continued for some time. It appears to me that the volume of the spleen decreases even on the day of the administration of the quinin, although in some cases it becomes a little larger; on the third day the decrease is quite material and steadily continues during the following days. If an originally marked swelling of the spleen remains at a medium stage of enlargement after some days, I find it serviceable to repeat one-half or an entire dose at once; in fact, to determine the repetition of the doses and their sizes as much according to the size of the spleen as according to the symptoms of the fever, to insist, therefore, absolutely upon some larger doses with long intervals. These methods of employment have the advantage of greater rapidity, certainty and cheapness over the use of quinin in many smaller isolated doses; the latter cause the attacks to be shorter and weaker, but they do not inhibit them until late, and sometimes not at all." We note, accordingly, that Griesinger followed absolutely the principles of dosage as determined by Torti. Regarding the time of administration, Griesinger recommended giving quinin only during the apyrexia some time before the occurrence of the attack, in short, immediately after the termination of the paroxysm. The onset of the intermissions should not be awaited in the pernicious fevers. "The remedy in this case should at first be given during the remissions of the fever and, when they are absent, at any time, in large doses; 30 to 50 grains per day should not be feared in such cases. Maillot (*loc. cit.*, page 397) in one case administered 180 grains in twenty-four hours with recovery of the patient."

In districts in which the cause of the fever acts continuously and to a marked extent, Griesinger advised, by way of prophylaxis during the period in which, with the continuance of the fever, a new attack would have occurred, "either to repeat the relatively large single dose on the fifth, seventh and tenth days or to take quinin tincture, powder, or quinin with bitter vegetable remedies and wine every day in moderate doses."

In cases in which the remedy could not be given per os, he considered the

administration of an enema of dissolved quinin sulphate, with the addition of sulphuric acid, at 4 to 10 grains per dose, indicated. "It acts in this manner at least quite as rapidly as by the stomach." Besides he believed hypodermic injections, which at that period were recommended by different authors, to be in order, according to the urgency of the case, 5 to 10 grains per dose.

Of quinin salts he recommended, besides the sulphate, only quinin tannate owing to its being less bitter. "Muriate, valerianate, citronate, tartrate or even urate, and camphorate combinations do not deserve further trial." He rejected all the other alkaloids of Peruvian bark and its salts, as well as all the other remedies recommended for malaria, tinctures of various kinds, as for instance, Warburg's, which contain, besides quinin, aloë, camphor and opium, the numerous substances obtained from plants, such as piperin, beerin, salicin, cnicin, gentianin, narcotin, belladonna; further, common salt, sulphid of magnesium (Polli), arsenic and iron, alone or in combination with quinin, because their effect is a very doubtful one, at any rate a much more uncertain one than that of quinin, namely, because they were efficacious only in proportion to the quinin contained in them. "If we observe that the most heterogenous substances and effects, tartar emetic, coffee, cupping, and turpentine liniments, oak bark and spider webs, warm and cold water, strict fasting and the contrary, as well as also mere suggestions to the imagination, produce modifications in the appearance of the attacks, without possessing any action upon the original process, the manifold recommendations and their rapid passing away are easily conceivable. If a remedy against the fever is to be of actual value, its effect must become manifest upon the disturbed vegetative processes, especially upon the spleen, as much as upon the paroxysms of the fever."

These words of Griesinger should be borne in mind by all who even to-day come forward with new remedies against the fever without having tested their efficacy in a large number of patients. What does it signify if, for instance, Peter Buro recommends alkaline nitrates, especially sodium nitrate in doses of 1 to $1\frac{1}{2}$ grams, as specific remedies against malaria, basing his claims upon the favorable effect in half a dozen cases of tertian and quartan fevers? Such cases recover frequently enough without any medication at all! Canalis, in the military hospital of Rome, saw the first cases of tertian and quartan fevers admitted in June recover spontaneously, after one or two attacks, without the administration of quinin! The fact that spontaneous recovery from these fever forms is by no means rare must, therefore, never be forgotten in passing an opinion upon a remedy against the fever. The apparently successful cures with every possible remedy may be explained in such a manner; for instance, the so-called eating away of the fever with large quantities of indigestible puddings or sour potatoes, etc., in Würtemberg, which sometimes, as Griesinger states, cause a rapid decided cessation of the paroxysms, and the favorable effect of abundant taking of buttermilk in Upper Silesia, "according to which," as reported by Virchow, "as people assured me quite generally, the fever very soon receded."

After having recognized the best remedy for the fever, its dosage, and the most favorable method and period for its administration, a decided further advance in the therapy of malarial diseases could hardly have been expected.

And yet, further investigations have brought about important improvements in the method of treatment, especially in regard to the certainty of success in the individual case. This progress is connected with the recognition of the etiology of malaria and in particular with the discovery of the manner in which quinin influences the malarial process, for even in 1872, Briquet wrote, in his reflections upon the action of quinin salts: "*La spécialité d'action du Quinquina étant bien déterminée, la raison indique que son influence ne peut s'exercer que sur le système nerveux. Il ne reste plus qu'à rechercher de quelle manière se produit cette influence.*" Chapéron believed he had demonstrated in the laboratory of Fick in Würzburg that quinin reduces the reflex irritability. As the nature of the fever was regarded as an increase of reflex irritability, the action of quinin was thoroughly explained. The fundamental investigations of Binz regarding the effects of quinin wrought a complete change in the conception of the effects of quinin. Binz demonstrated that quinin, on the one hand, is a very powerful poison or toxin to lower protoplasm, and, on the other hand, if used in the ordinary doses does not exert any influence upon the nervous system. He concluded, therefore: "Quinin does not act upon the nervous system, as has been generally assumed until now, but it suppresses the malarial fever and all its symptoms, and, consequently, also the intermittent attacks, by paralysis of its cause which is probably a very low form of organism." In 1875 he wrote (*Das Chinin*, page 18): "All facts lead to the assumption that the infective cause is itself paralyzed by quinin, whether it be a lower organism which in a periodical manner swarms from its breeding place, the lymph organs of the spleen, as a new generation and by vaso-motor irritation to which it regularly gives rise, causes the symptom-complex fever to appear as an expression of this action, or whether it be a chemical, soluble poison that by an accumulation of irritation produces periodical disturbances besides transitory decomposition of organic albumin in large amounts, causing an increasing rise in temperature."

The lower organism postulated by Binz was subsequently found by Laveran. Laveran was the first to investigate the action of quinin upon this organism in that he mixed a drop of greatly diluted quinin solution with a drop of malarial blood and examined it under the microscope. He saw that the movements of the flagella ceased and that the blood parasite became a cadaver. Dock, in Galveston, also saw the plasmodia become motionless under the influence of quinin, ceasing to send forth flagella. Laveran then concluded, from direct observations and also from the disappearance of the parasite from the blood of patients treated with quinin that the parasites in the blood of the patients were destroyed by quinin. Then the important question arose: "What concentration of quinin is necessary to destroy the parasites in the blood?" Binz found that quinin kills the paramecium, with a solution of 1 to 400 immediately, of 1 to 1,000 in two minutes, of 1 to 10,000 in two hours. In his experiments on fresh water ameba and various kinds of infusoria, he had found that, in order to cause a cessation of ameboid movements upon the warmed object carrier a lower proportion than 1 to 4,000 must not be employed. He had determined, besides, that the inflammation in the mesentery of the frog, which accompanies the emigration of colorless blood corpuscles, only decidedly ceases upon administration of quinin in the proportion

of 1 to 4,000 to 5,000 of its body-weight. Assuming that the susceptibility of the ameba of malaria is equal to that of the fresh water ameba, that is, of the colorless blood corpuscles of the frog, it is necessary, therefore, that quinin attain a concentration of $\frac{1}{4000}$ to $\frac{1}{5000}$ in the blood to injure and destroy these parasites.

The quantity of blood of a human being weighing 130 pounds, is approximately 5 kilos, or 5,000 grams. It is necessary, therefore, that 1 gram of quinin circulate in the blood to have the desired effect. To obtain as rapidly as possible an action of the quinin, Guido Baccelli injected neutral solutions of quinin hydrochlorate (quinin hydrochlorate 1.0, sodium chlorid 0.75, distilled water 10.0) into the veins of numerous malaria patients, especially in severe pernicious forms in which the other modes of absorption had proven to be insufficient, and he found that doses of 10 to 30 centigrams were entirely insufficient, that doses of 40 to 60 centigrams showed a better effect, which were not completely satisfactory, that doses of 1 gram, however, which corresponded about to the concentration of 1 to 5,000 determined as fatal to infusoria by Binz, had an infallible therapeutic effect. Of very particular interest are the results of blood examinations undertaken by Baccelli in order to learn the mechanism of the action of quinin. He reports as follows: "We have undertaken detailed investigations in that we observed the blood one-half hour and each succeeding half hour after the intravenous administration of a gram of quinin. We did not observe any material modification during the first six hours either in number or in form or in the ameboid motility of the parasite. We only thought that we noted, during the first two or three hours, a greater activity of the movements. However, it is certain that almost all parasites could be considered as having disappeared after twenty-four hours without our being able to determine previously a phase of retrograde formation or destruction. The pigmented and crescent-shaped varieties of Laveran remained visible for several days after the intravenous introduction of the quinin and after the disappearance of the fever. It is absolutely necessary to state that, according to the relations between the alterations of the blood and the fever, only the ameboid form was found to be continually associated with the febrile period, whereas the developed forms, the semilunar and pigmented ones, occurred also during the afebrile intermission in such a manner that the condition of the blood in these various forms proved to be identical in patients suffering from quinin poisoning and in those that were not affected by the latter." Baccelli then continues, "That quinin is not capable, even with a dose of 1 gram, to abort the attack of fever if introduced (into the veins) at the onset of the latter or even three hours before," that quinin administered during the acme of the fever will not accelerate the crisis, but that "quinin introduced during the decline or toward the end of the attack either absolutely forestalls the succeeding attack or at least reduces its intensity very materially."

These observations proved most decidedly that quinin in the concentration as employed surely did not kill the endoglobular ameboid parasites, but that, nevertheless, the small ameba disappeared after twenty-four hours, whereas the larger pigmented forms and crescents were present in the blood also after the disappearance of the fever. How could this action of quinin be

explained? Baccelli found that quinin, upon intravenous injection, could be demonstrated in the urine as early as fifteen minutes later and, furthermore, still after twenty-four hours. With subcutaneous injection he was able to demonstrate it after ten minutes up to forty-eight hours and upon administration per os from twenty-four minutes up to thirty-two hours which conforms to the statements made by Binz, Schwenger and Kerner. Quinin, therefore, is present in the blood from one to two days after powerful doses of the drug introduced in any manner whatever. Binz, accordingly, arrived at the conclusion that quinin, if it remains long enough in the organism, has ample time to weaken the parasites and to paralyze them. "It is not necessary for the drug to kill them, for weakened parasites are overcome by the organism."

Accordingly, the action of quinin was then considered to be dependent upon a weakening of the parasites, whereas the actual elimination of the same was left to the defensive powers of the affected organism. As leukocytes, which contain melanin, yes, even parasites, are frequently found in the blood of fever patients, the thought suggested itself, according to Metschnikoff's phagocyte theory, that the leukocytes were the agents which now absorbed the weakened ameba and then digested them intracellularly. According to the investigations of Lo Monaco and Panichi, the quinin would cause the plasmodia to leave the blood corpuscles into which they had entered so that now they could be destroyed by the blood plasma and the leukocytes. Yea, Vandyke Carter even expressed the opinion that quinin did not act directly upon the parasites but that it stimulated the leukocytes to increased activity.

But was the proof actually rendered that quinin really weakens the parasites in the blood of patients? The investigations of Baccelli are not in favor of this statement. He had not observed any of these signs during six hours in which continuous observations of the blood were made and during which the concentration of quinin in the blood is greatest.

Another conception of the action of quinin was brought about by the investigations of Romanowsky with the aid of the staining methods discovered by him, by means of which the most important constituents of the parasite, the chromative part of its nucleus, was rendered accessible to observation. Romanowsky assumed that if quinin killed the parasite, the death of this organism was bound to manifest itself in processes of destruction which would resemble the processes of dying of any living cell in general. It has been demonstrated, according to the investigations of Arnheim, Podwjssozky, Lukjanow, Pfitzner, and others, that the destruction of the cell is always accompanied with the morphological change of the nucleus, the chromative structures of the nucleus disintegrate into coarser flakes, then into spheric granules and these latter become gradually smaller until they finally disappear entirely. The process of "nuclear degeneration" so-called by Arnold takes place.

Romanowsky, examining the parasites of malaria according to his method, on the days following the administration of quinin, observed the following: Free forms were found only when quinin had been administered two to three hours before the attack, "when, therefore, the drug had not had time to display its full effect." The parasites were round, without shoots, the nucleus intensely stained, but the halo around the nucleus was not distinctly pronounced. The

shoots in the endoglobular parasites were noted to be more blunt, the nucleus large, swollen in a manner, of palest stain, the areola scarcely being recognizable, the protoplasm otherwise stained a uniform blue, whereas he found it more reddish in the healthy parasites. But the most conspicuous changes were found in the pigmented parasites, the development of which had advanced further: "The parasite is of a round (quiet) form, the protoplasm no longer exhibits any signs of ameboid movements, does not have any shoots and is uniformly stained; the pigment is regularly distributed; in some cases it is seen entirely in the periphery which is not observed in healthy parasites. In place of the nucleus we note a fine dotting which, however, does not depend upon the pigment but which represents a disintegrated nucleus; this dotting, in intensely stained preparations, is of a weak, scarcely indicated, violet stain and occupies the entire space of the nucleus which can be recognized from a paler shade of the staining. Of the light areola no trace is left; the nucleus in a manner gradually passes into the protoplasm. In the stages of transition between the just-described form of the parasite and the previous one, an area can be distinguished which is of a brighter stain—the residue of the nucleus, in which violet, irregularly deposited threads are visible, and upon close observation, prove to be mostly composed of fine dots. This is not at all noticeable in the fully mature parasites in which the signs of fibre metamorphosis of the nucleus should be most distinct.

"The quinin effect in the sporulation forms is manifest in that the protoplasm is also stained uniformly; the nucleus stains most intensely and is entirely without areola. The effect of the quinin, therefore, is most markedly manifest in the adult endoglobular forms, the nuclei of which disappear entirely, so that, therefore, the parasite appears as a uniformly bluish-gray pigmented area upon the blood corpuscle which is stained a pale eosin.

"The symptoms of destruction are more obviously manifest in the less compact nucleus of the adult parasite than in the compact nucleus of the younger."

Accordingly, the parasite is subject to all known laws of the dying cell.

Romanowsky concludes: "As all these manifestations take place only after the administration of quinin we are justified in saying that the latter actually kills the parasites as all the characteristic manifestations of the destruction of the cell take place in the organism."

These observations of Romanowsky in the tertian parasite determine therefore, that quinin causes the destruction of the parasite of malaria. Parasites, in which the chromative constituents of the nucleus have been destroyed, are no longer capable of propagation; they are no longer able to produce two generations and are, therefore, destined to perish. The prevention of endogenous propagation also inhibits the appearance of new attacks.

This explanation harmonizes throughout with the old practical experience that it is possible to prevent an attack of fever if a powerful dose of quinin is given during the interval of the febrile attacks at periods of ten to twelve hours previous to the expected attack; however, it is not in accord with the fact discovered by Baccelli that he was not able, by the injection of 1 gram of quinin into the veins three hours before the expected attack, to prevent the latter, whereas the curative action of this method of treatment was quite excellent.

Of great significance for the understanding of the action of quinin and for the correct employment of quinin were the investigations undertaken by Golgi, the discoverer of the typical endogenous development of the quartan and tertian parasites. Baccelli made his experiments, as it appears, exclusively in the parasite of tropical malaria, which, at that time, was not yet sufficiently recognized, whereas Romanowsky utilized the parasite of tertian fever in his observations. Golgi studied the action of quinin at first in the typical quartan fevers which were most numerous and at his disposal, but then also subsequently in the tertian fevers and in those forms which were accompanied with crescents. The actually classical investigations in quartan fever furnish the following absolutely unambiguous results: Quinin, given in the usual dose (1 gram in two doses of half a gram each, the second one to be taken one-half hour after the first) six hours before the expected attack, does not prevent or influence the latter, even larger doses, 0.75 gram and half an hour later 0.5 gram subcutaneously, three to five hours before the attack, and twice the dose, two grams in three doses with intervals of twenty minutes each, administered four hours before the attack, are without effect upon the intensity of the latter. The continuous microscopical examination of the blood showed that sporulation always took place in the typical manner. An ordinary dose of quinin, taken eight to ten hours before the attack, distinctly lessened the latter but did not prevent it, but the patients were cured in every instance, i. e., no attacks occurred again and mostly no recurrences.

When quinin was given on the *first day of apyrexia*, the attack that was expected was either prevented or only weakened and postponed. Then followed slight or irregular attacks or intermissions, but, finally, marked relapses.

Given on the *second day of apyrexia* the effect was much better and much more marked than upon administration on the first day.

Golgi achieved excellent results also when he administered 2 to 3½ grams, distributed in smaller doses in the course of both days of apyrexia—in 6 cases 1 recurrence after ten days. The conclusions which Golgi drew from these observations were as follows:

“The malarial parasites feel the effect of quinin in varying degrees, according to the stage of development in which they are; to express it exactly, they perceive this effect with decreasing rapidity and intensity in the following order:

1. The youngest forms which result immediately from the segmentation process or from the formation of spores; these do not appear again as young endoglobular forms to prepare a further attack. In that they are affected at the moment of their formation, they are in the surest manner killed by the specific for malaria.

2. The forms of more advanced development which are almost mature (with almost complete absorption of the globular substance), but in which the process of segmentation and differentiation of the protoplasm, that process which terminates in segmentation, has not yet begun.

3. The young forms which have already entered the red blood corpuscles but which, as they are only at the onset of development, are enclosed and, so to say, protected by a thick layer of globular substance.”

Accordingly, after Golgi's conception, the very young parasites which have just become liberated and those which are immediately before the stage of segmentation almost entirely filling the blood corpuscle, are especially sensitive; the former are killed directly by the quinin, the latter are prevented from sporulating.

In *typical tertian fevers*, which were not as numerous at the disposal of Golgi as quartan fevers, he determined again, as in quartan fever, that an ordinary dose of quinin, taken four hours before the attack, did not prevent the attack but caused permanent cure, that, therefore, as in quartan fever, sporulation which had already commenced at the onset of the effect of quinin was not prevented but that the young forms resulting from the latter were surely killed. He was able to determine, in regard to the endoglobular forms of tertian fever, a much greater susceptibility to quinin than in the endoglobular forms of quartan fever. He believed that this difference, this increased vulnerability, of the endoglobular tertian parasite, might be due to the peculiar changes which the blood corpuscles harboring the tertian parasite show from the beginning. Their swelling, the disappearance at the rapid destruction of their hemoglobin contents are the causes of quinin acting much more promptly through the red blood corpuscles upon the parasites.

The statements of Golgi regarding the effect of quinin in cases of fever accompanied with crescent forms, the developmental cycle of which was not yet known to him, are much less distinct, he emphasizes only "that these forms, similar to the lasting forms of schizontes, are almost insusceptible to the action of the ordinary agents." The infection had not disappeared in many cases after 10 to 12 grams of quinin given in the course of eight to ten days, although the attacks of fever failed to appear. He concluded from the periodic invasion of small endoglobular ameba that were observed in these cases during the period of fever, that a sporulation took place also on the part of the crescent structures and that, therefore, it is a thoroughly justifiable idea to believe "that the continued use of quinin in these cases is also capable of killing the young forms which, by a process the loss of which was not determined as yet, invaded the blood from time to time in longer or shorter intervals."

Regarding the flagellated forms, Golgi was not able to determine an influence of quinin either upon the occurrence of these forms or upon the manner in which they presented themselves or upon their movements.

The phenomena which Golgi observed in the parasites in consequence of the action of quinin are as follows:

"In the endoglobular forms: fine granulation of the pigment, metallic reflex of the same, a certain opacity of the protoplasm, tendency of the enclosing blood corpuscle and of the enclosing parasite to shrink, lessening of ameboid movement (in tertian parasites), transformation into rounded, sharply defined, immotile structures, the pigment of which is distinguished, by its peculiar reflex and by its tendency to conglomeration, from that of normal parasites (in the tertians); in the more advanced phases of the parasites: occurrence of peculiar transparent forms with actively motile pigment, larger than red blood corpuscles—degenerated forms, cadaver forms, and, finally, irregularities in the mature forms and in sporulation—smaller, slight-

ly sharpened spore forms, irregular accumulation of pigment, smaller number of spores.

Later observers, Mannaberg, Marchiafava, Bignami, have confirmed these changes observed by Golgi in the action of quinin upon quartan and tertian parasites, and have in part rendered them more complete. Thus, the endoglobular parasites of tertian fever are said to lose the ability of staining of their nuclei and to obtain a friable protoplasm so that they are visible as fragments within the blood corpuscles. Especially, Ziemann emphasized particularly that the body of the protoplasm is torn into "a number of individual, irregularly formed fragments" by the quinin, whereas the chromatin does not appear to be injured. However, he also stated that the parasites in the same stage of development, which are subject to the influence of quinin, did not present equally marked changes.

Schaudinn arrived at very similar results in examining the action of quinin upon tertian parasites, with the aid of the Romanowsky stain, the most endoglobular schizontes were stained more dimly than normal, without distinct contours, vanishing, distorted in shape, the caryosoma which was mostly globular was changed and shrunken. The older stages of growth were shown to be similarly torn and diffuse. Schaudinn found the nuclei of the latter also torn as well as the plasma. But little altered were the reproduced phases which were multiplied in the nuclei; markedly damaged again were the terminal stages of schizogonia; the merozoites were stained diffusely and torn (see colored illustration).

The half-grown sexual forms were changed the same as the schizontes, but the full-grown gametes appeared uninfluenced.

Regarding the consequences of these observations, Golgi has defined them accurately as follows: It is necessary in quartan and tertian fevers, according to the excellent classical description, to administer quinin, three, four and five hours before the attack so that the young generation of parasites is affected in the nascent state by the quinin in proper concentration, as, according to the investigations of Kerner, a relatively large quantity of the quinin taken circulates in the blood during the first six hours after it is administered. The accomplishment of a disorder in the development of the endoglobular parasites, the disturbance of the process of sporulation, is in a certain relation to the size of a dose of quinin given; the effect is obtained much more surely with larger doses. If, therefore, the administration of quinin takes place in large doses during the entire period of apyrexia, it is frequently not only capable of preventing the first attack but also of annihilating the infection. Golgi concludes that it certainly follows from the entirety of the observations "that the most rational means for a certain accomplishment of the extinction of the infection is not to be effected with one administration of quinin but that this remedy must be continued for several succeeding days."

Golgi considers the therapy of the quartan and tertian fevers to be concluded with the above, however, not that of the varieties of fever with crescents and with the small endoglobular parasites. He believes that, for these, he could for the present only repeat the direction to continue for weeks the daily uninterrupted administration of quinin in medium doses.

But the therapy of these forms, in particular, is of the greatest importance

for the tropics, in which they produce not only the greatest number of the affections but also the attacks of so-called pernicious fever. The pronounced intermissions which are otherwise an indication for the administration of quinin are absent in these forms. It is frequently necessary to suppress the subsequent attack as it may lead to a lethal termination. As a certain norm did not exist, the physicians of the tropics administered quinin at random in every case and, the ordinary large doses, 3, 4, yes, even more grams in one dose, of quinin frequently failed. To have checked this “wild quinin therapy” and to have discovered the correct rational treatment of this form of fever, tropical malaria, is the great merit of Robert Koch. As stated previously, Koch claimed at first that the normal untreated tropical fever always runs its course as tertian fever, only with the difference from ordinary tertian forms that the attack extends, instead of over four to eight hours, over about thirty-six hours and, further, that the course corresponds to the development

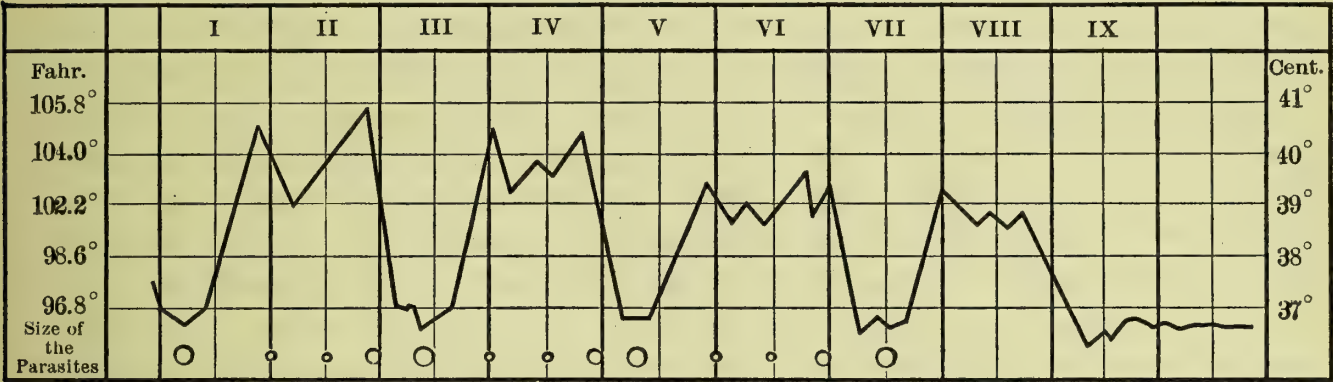


FIG. 14.—CURVE OF TROPICAL FEVER. (After Robert Koch.)

of the small, ring-shaped parasites. Usually no parasites at all are found during the rise of the fever; but if the blood is examined after the fever has been at its height for some hours, only the small rings are found, the breadth of which is about one-sixth of the diameter of the red corpuscle. These are found at the acme of the entire attack as long as the temperature remains high. Slightly larger rings are found toward the end of the attack, but only after the temperature has gone down and the attack has entirely terminated does a great number of large rings occur, of which one side of each is crescent-like and thickened. They can be demonstrated in the blood for about twelve to sixteen hours, to disappear with the end of apyrexia and to pass through their sporulation in the internal organs during the following twelve hours, in consequence of which the smallest rings again make their appearance. The large rings grow materially in the internal organs before sporulation, as sporulating forms which were found, for instance, in the capillaries of the brain, occupy almost the entire red blood corpuscle.

Koch is of the opinion that quinin is not capable of killing the parasites but that it only prevents their development. He intends, therefore, to administer quinin in such a manner as to check sporulation. He says: “If we succeed in preventing the parasite from sporulating, it does not produce a new generation; its allotted time is also at an end; it dies therefore, and thus the patient is relieved of his parasites.” Koch, therefore, means to destroy the parasites with the quinin before they sporulate.

He considers that the correct time to administer quinin is as soon as the large rings occur in the blood. This is possible, as Koch emphasized particularly, solely by the microscopical examination of the blood, but then with certainty and ease. "Then, as a rule, one single dose of quinin is sufficient to obliterate tropical malaria quite as surely, I might say still more surely, than other domestic tertian fevers." It is extremely difficult, however, to decide whether in tropical malaria, with such a method, as Koch believes, sporulation is prevented or whether the young generation is destroyed, as only one phase of the life of the parasite takes place in the peripheral blood. It is possible that both assumptions are correct, that the sporulating parasites are torn by the quinin, and that also the young forms which are produced by segmentation are destroyed.

It is probable that the parasites of tropical malaria do not on principle act differently than do the parasites of quartan and tertian fevers. It is not possible, according to Golgi's investigations, with a powerful dose of quinin, administered four to six hours previous to the attack, to suppress the latter, but it is possible to cure the patient thereby. It appears that similar conditions prevail also in tropical malaria. Ruge says: "Even tropical malaria is not frequently aborted with 1 gram of quinin, even if this gram is administered at the correct time during the appearance of the large tropical rings," and, further, "Although the subsequent attack can usually not be prevented by a single dose of quinin, even if it be administered at the correct time, yet a complete intermission is always obtained through it. Accordingly, a powerful dose given before sporulation will not always prevent the latter even in tropical malaria—for the attack takes place—but it is probable that the young parasites are also destroyed in tropical malaria in the nascent state.

Maurer assumes, by reason of his previously mentioned studies of staining methods, that the parasites of tropical malaria at first, as "external schizontes," inhabiting the surface of the erythrocytes, grow upon the latter to large rings, but then disappearing from the peripheral blood, enter the interior of the blood disks in the capillaries of the internal organs, in which the current velocity of the blood is greatly lessened, then to segment as "internal schizontes." Maurer maintains, regarding the effect of quinin, that it acts most rapidly and most intensely upon the young segmentation forms, the merozoites, and upon the external schizontes, that it also destroys still younger internal schizontes but only weakens older ones in their vital energy and prolongs the duration of their development. Quinin, to be effective, should, therefore, be present in the blood during the external life of the schizontes. This object is accomplished if quinin is administered according to the directions of Koch.

As sporulation extends over quite a long period of time in tropical malaria, it is advisable, in order to affect as many as possible of the parasites sporulating at various hours and their products, to administer quinin repeatedly, commencing with the onset of the occurrence of the large rings.

According to the above, with Ruge, we may sum up the general directions of the quinin therapy as follows:

(A) In the ordinary intermittent fevers, 1 gram of quinin must be given (small children should receive as many decigrams as they are years of age,

R. Koch), four to five hours before the expected attack, and the same doses should be repeated at the same hour for six subsequent days.

(B) In tropical malaria, during defervescence, at the appearance of the large tropical rings, also 1 gram of quinin must be administered and the dose should be repeated after four hours, at once or divided into two parts with an intermission of four hours. On each of the six succeeding days, at the same hour, 1 gram of quinin must be given.

However, the above-described quinin therapy does not by any means terminate in cure in quite a number of cases, especially of tropical malaria. Isolated parasites frequently remain alive in spite of quinin; possibly those that are enclosed by cell structures in the internal organs. It seems that they are in a quiescent condition for weeks, for months, sometimes for over a year, from which they are aroused to renewed activity by certain factors acting upon the patient, thus, for instance, by disturbances of the heat regulation of the body, by refrigerations, drenchings, a cold bath, seasickness, and even by violent mental excitements. Absence from the malarial district, change of climate, sojourn in the mountains, do not prevent a return of the attack. To explain recurrences after a long period, Grassi has set up the hypothesis that the sexual gametes intended for the further development of the parasite in the anopheles are eventually capable of segmenting parthenogenetically in the human blood and that the new attacks are produced by forms which arise in such a manner. He referred to analogous occurrences which were demonstrated in numerous protozoa; thus, in the *adelea*, *trichosphærium*, *volvox*, and upon observations of crescents, as we have stated before, so-called segmentation forms were noted by Grassi and Feletti, Mannaberg and Ziemann. As we know from experience that the gametes are extremely resistant to quinin, the appearance of recurrences could well be explained by parthenogenetic increase of the gametes in spite of quinin treatment being continued for a long period of time. The parthenogenetic origin of the recurrences has been rendered very probable by the latest investigations of Schaudinn who, as previously stated, has proven the origin of new endogenous generations of parasites from macrogametes of tertian fever, and of Maurer, who has also seen in the parasites of tropic malaria parthenogenetic appearance of fresh young parasites from crescents.

The question is now, how to act in regard to these relapses; are we to suspend treatment until they have appeared or shall we attempt to prevent them?

Naturally, every patient desires to be completely cured of his fever, but it is of the greatest importance for the prophylaxis of malaria that he be entirely relieved of his parasites.

For all these reasons it is necessary not to restrict ourselves to treating the new recurrence, but we must endeavor to prevent relapses entirely. Koch has given his particular attention especially to this important question. He acted upon the observation that the incubation period of malaria lasts ten days on the average. If, therefore, some parasites had escaped the quinin employed for cure, they might have multiplied sufficiently after ten days to cause a new attack.

Therefore, he administered to a patient who had recovered from the attack 1 gram of quinin every tenth day; that was not sufficient. Accordingly, he

shortened the interval to seven and then to five days. Although the number of recurrences became less, there were still too many.

He therefore adopted another method and gave the quinin in intervals of ten days, but equal doses on two succeeding days. Now the recurrences failed to appear in the greatest majority of cases. A lessening of the intervals to eight or to seven days, or, still better, an increase of every dose to $1\frac{1}{2}$ grams, proved to be efficacious in particularly obstinate cases.

No recurrences took place in those cases in which the patient was given $1\frac{1}{2}$ grams on two successive days, with intervals of nine days. The after-treatment, however, must be continued for at least two months.

The determination of the correct time for the administration and the proper doses of quinin by no means solves the problem in practice regarding the correct treatment of malaria.

The physician must also satisfy himself that the quinin which is properly administered to the patient actually reaches the point at which it is intended to act—the blood.

Quinin and its salts only dissolve readily in acid media, not so, however, if the reaction of the latter becomes alkaline, only in solution are they absorbed rapidly and surely.

The normal stomach produces hydrochloric acid, therefore, keeps the salt administered per os in solution, that is, it dissolves the salt that is not yet in solution. If the patient suffers from gastric disturbances which impair or prevent the normal production of acid, no salt that is introduced in substance into the same will be dissolved.

The resorption of fluids takes place principally from the stomach, and only from the stomach does the resorption of quinin occur. If quinin passes the stomach without being dissolved and resorbed it reaches the intestine, which has an alkaline reaction, and its effect is lost. After the introduction of watery solutions, the production of hydrochloric acid commences, still more rapidly upon the introduction of food.

It is advisable, therefore, to introduce quinin into the stomach after some food has been partaken of, not, however, into a stomach which is greatly filled with food, and best in a slightly dissolved condition. Koch advises, for instance, to place 10 grams of quinin into a water bath, slowly to drop hydrochloric acid upon it until it has dissolved entirely, then to wash the fluid into a measuring cylinder and to fill up to 100 cc. Ten cc. of such a solution contains 1 gram of quinin. He advises, as the best corrective of the intensely and disagreeable bitter taste, to take a piece of sugar immediately afterward. The drinking of alkaline mineral waters and, also of coffee, after taking quinin must be avoided. It would be more advisable, especially in disturbed function of the stomach, to drink some diluted hydrochloric acid afterward.

As the disagreeable taste is so repugnant or becomes so to many and the patients cannot be prevailed upon to take quinin in solution, it may be administered in capsules. The administration in gelatin capsules has come into special favor recently. The covering in cigarette paper, which is particularly practised in the tropics, should be rejected, because the paper covering frequently does not open; the administration in pills is also not advisable, because they dissolve in the stomach but very slightly if at all. Very practi-

cal is also the employment of quinin tablets, which are well preserved in the tropics and which easily dissolve in the stomach, especially if some water containing hydrochloric acid is taken afterward.

The attempt to manufacture tasteless combinations of quinin were futile for a long time; these preparations either contained too little quinin or they did not dissolve sufficiently in the gastric juice. These attempts were more successful recently. New preparations have been brought into the market under the name of euchinin, saloquinin, and aristochin, of which euchinin has been tested especially by Celli.

Dreser considers aristochin to be the most serviceable combination. It is dichinincarbonacid ester, manufactured by the Farbenfabriken von F. Bayer & Co., in Elberfeld; it contains 96.1 per cent. quinin base, forms a white powder *without perceptible taste*, and, according to Stursberg, is well absorbed by the stomach without irritating the mucous membrane of the same.

Its toxic action upon protozoa, according to Dreser, is said to be twice as great as that of quinin. On the other hand, the general toxicity of the quinin molecule, in cold-blooded and in warm-blooded animals, is most pronouncedly decreased in the form of aristochin. Stursberg found it serviceable in whooping-cough of children, in doses up to 0.3 grams three times daily. The future will tell whether it will be efficacious against malaria.

If the introduction into the stomach is hindered by countless insurmountable difficulties, quinin might be introduced by enema. According to the older statements of Griesinger, and to the latest investigations of Kleine, it is very well absorbed by the rectum.

The quantity of quinin hydrochlorate excreted in twenty-four hours in the urine after the administration per enema amounted to 17 per cent., whereas 35 per cent. appeared in the urine after the administration per os. The signs that the quinin has been absorbed, tinnitus aurium, nausea, etc., occur in the same manner after administration per enema as after that by the mouth. However, the administration per clyster, after a preceding enema intended for cleansing, is rendered considerably more difficult in that an unbearable desire to defecate is very apt to occur, even if only 2 grams are given in 100 cc. of water. Kleine, however, employed successfully additions of 20 drops of opium or cocain and at the same time prescribed belladonna suppositories.

Subcutaneous injections of quinin are recommended and much employed in practice. It is necessary to administer the drug subcutaneously (Koch) especially if it is important, in the presence of threatening symptoms, to cause a prompt action of the quinin. Kade's tubules are in great favor; they contain a sterilized solution of 0.5 gram chin. bimur., or bimur. carbamid. in 1 cc. of water. Several cases of tetanus have been observed by English physicians, in the tropics, after subcutaneous injection of quinin. P. T. Manson especially called attention to this danger. It is necessary, therefore, that the injection be made with antiseptic precautions. Five minutes' boiling of the solution to be injected is sufficient to destroy with certainty the spores of tetanus; then the danger is not even present in the tropics, as is proven by the extensive experiences of Benson and others.

Severe local pains and swellings, even cutaneous necrosis, were frequently

observed as consequences of subcutaneous injections. These disagreeable conditions are caused, according to the experimental investigations of von Fleischl, by the varying susceptibility of the skin to the different preparations. He reported that chin. carbamid. is not very well borne. R. Fervers saw necrosis of the skin the size of a lentil to that of a two-mark piece, besides cases without reaction. Quinin bisulphate left pains upon pressure, hard nodes, and subcutaneous cicatrices. Quinin bimuriate was always excellently borne, as he was able to determine in harmony with H. Holland. In about 1,000 injections which von Fleischl made in human beings in more than twenty years, neither an abscess nor even redness of the skin occurred over the injection. He advises that after the injection, there be continued rubbing at the point of injection for some time, to distribute the solution as much as possible in the subcutaneous cellular tissue. According to his extensive experiments regarding the solubility of quinin salts, he found the following proportions:

One gram quinin bimuriate is dissolved in 0.66 water—the solution remained clear for weeks at 2.5° C., in 0.4 heated water—the solution remained fluid for ten minutes, before it congealed to a transparent mass (at 2.5° C.);

One gram of quinin bisulphate heated in 2.5 water remained dissolved for three-quarters of an hour at 12.5° C.; it dissolved in the proportion of 1:9;

One gram quinin muriate dissolved in 10.0 water upon heating, remained dissolved from two to three hours at 12.5° C. At 18.75° C. it dissolved in the proportion of 1:34. In the solution of 1:4 the salt remained dissolved for twelve minutes at a temperature of 12.5° C.

One gram quinin hydrobromate dissolved easily in 4.0 of water upon heating. The solution became cloudy even upon blowing over it, due to the cooling. A portion of the salt precipitated even in a solution of 1:12½ upon cooling having scarcely commenced.

Owing to its rapid precipitation, von Fleischl considers this salt fully suitable for subcutaneous injections. He never saw a quinin salt precipitated in the body of a rabbit if he examined the point of injection fifteen to thirty minutes after the injection. The tissue within reach of the injection and beyond was extremely succulent, the fluid entirely clear.

The more recent investigations of Bluemchen are not quite in accord with the above results of von Fleischl. The former reports that the bimuriate in Kades' tubules as well as solutions containing alcohol and hydrochloric acid, produced infiltrations which remained painful for weeks and which sometimes led to cutaneous necrosis; but that quinin muriate dissolved in hot water 1:1 and cooled at the temperature of the body does not cause any pain after the injection and that, if only ½ gram is injected into one part of the skin, infiltrations or necrosis never occur, such as can be observed after those of more than 1 gram. Tinnitus aurium and vertigo which become noticeable after about thirty minutes are never serious. ½ a gram subcutaneously, according to the opinion of competent physicians, corresponds to 1 gram per os in efficacy.

Kleine, who investigated the excretion of quinin by means of the reliable method described by Hager—precipitation with picric acid, decomposition of the alkaloid picric acid with caustic potash and absorption of quinin with chloroform—found to his surprise that, whereas 17 per cent. to 38 per cent., on an average 25 per cent., were excreted in the urine when quinin was taken

per os, only 11 per cent. could be found in the urine after subcutaneous injection of $\frac{1}{2}$ gram of quinin bimuriate. Experiments in dogs showed that an excretion by the feces took place only in very small amounts. The slight excretion can be explained very simply: "Quinin injected subcutaneously, to a great extent precipitates at once at the point of injection; sometimes it is found after weeks, flattened in the fissures of the tissue."

This explanation is in contradiction to the observations of von Fleischl. This slight resorbent property contrasts also with the general promptness of effect of the subcutaneous injection which is also acknowledged by Koch. On the other hand, the usually apparent fact that subcutaneous injections produced generally only slight, or no, quinin symptoms at all, may possibly be explained in such a manner.

Kleine believes that the excretion of quinin after subcutaneous administration is protracted for weeks and that, by the subcutaneous injections, "quinin deposits" are established in the body which are gradually diminished by the dissolving lymph current. This lasting action of continuous doses of quinin should be considered as of great importance both in prophylaxis and in therapy.

Quinin bihydrobromate, which von Fleischl, owing to its tendency to precipitation upon cooling, did not consider serviceable, has recently been most successfully employed for subcutaneous injections and is highly recommended by Ferguson, the President of the British Medical Association. This quinin salt injected under the skin is said to be entirely non-irritating. Ferguson injects 3 grains dissolved in 20 minims of pure warm water at a dose, first under the skin of the upper arm, then under that of the thigh, later in the abdomen, or in the neck or between the scapulæ, on alternating days. The effect of these injections is said to be ten times as intense as that of equal doses taken per os. The subcutaneous injections of bihydrobromate cured patients in cases in which the tenfold dose taken daily per os was without effect. The secondary effects upon the head at the same time were much less than upon administering the drug by mouth. It was in no case necessary for Ferguson, although he treated almost one hundred malaria patients coming from the most malarial districts of the world, to give the dose of 3 grains = to 0.18 grams, more than six times to accomplish a cure. He advises making the injection two to three hours before the attack, to affect the spores; in chronic cases, it is immaterial at what time the injection is made provided it is done often enough: "I am convinced that there are few or no cases of malarial fever that will resist six subcutaneous doses of 3 grains each of quinin bihydrobromate." The future will tell whether these great expectations of Ferguson are realized. If it is correct that this quinin salt surely acts in such small doses from the subcutis, its introduction will mean a very extraordinary progress.

As yet, no reports exist regarding the absorption of quinin in intramuscular injections, which were highly recommended by A. Plehn and especially by Ziemann into the gluteal region, analogous to Lewin's injection cure of syphilis. Kleine only remarks that, in experiments on dogs, the tissue for a long time looks "very much injured" after intramuscular application. He probably injected a solution of $0.5 = 1:2$ water. Ziemann found that, with a

proportion of quinin to water of 1:1, the injections were very painful, at a proportion of 1:2 considerably less so, and that with a proportion of 1:3 the painfulness was but very slight or was not present at all. He always took the proportion of 1:4. He says: "I am in a position to recommend these intramuscular quinin injections most highly and most urgently in severe cases, owing to the relief to the stomach and owing to the extraordinarily prompt effects." [Walsford holds that intramuscular injections of quinin are much more satisfactory and less painful than hypodermic injections. He states that the latter when given in the arm may cause more or less prolonged paralysis of one or two fingers, while intramuscular injections are practically painless and the swelling caused by them soon disappears. Smyth, on the other hand, considers that the intramuscular use of quinin should be condemned; he has experienced bad results in his own person. If the drug is injected subcutaneously and the swelling is at once dispersed by gentle friction, no local damage will be done.—ED.] The intravenous injections which, as stated, Baccelli praised for the same reason, are not quite devoid of danger, and have become entirely superfluous in practice, owing to subcutaneous injection.

Unfortunately, however, the quinin salts possess, besides their brilliant curative actions, a great number of most undesirable, in part even secondarily dangerous, properties. Apart from the horribly bitter taste and the usual disagreeable manifestations of quinin poisoning, nausea, tinnitus aurium, difficulty in hearing, there occur in some individuals very disagreeable, even sometimes quite alarming phenomena: Congestions of the brain, cardiac palpitation, unrest, precordial anxiety, complete deafness, blindness, violent vertigo, vomiting, dyspnea, urticaria, eczema; phenomena which point to a special congenital susceptibility and intolerance to quinin. This intolerance may also develop gradually after continued use of the drug, especially in the tropics. But, finally, as has been convincingly demonstrated by Koch, in many individuals who pass a long period of time in tropical and subtropical districts, they possess the property of dissolving the blood corpuscles and thus they form the severe pathological picture of hemolysis which is generally known and feared under the name of "Schwarzwasserfiebers," blackwater fever, *fièvre bilieuse hémoglobinurique*.

Blackwater fever occurs frequently in certain tropical regions, thus in tropical Africa, especially in Kamerun and on the Congo, on the Senega, in Sierra Leone, on the Ivory Coast, in the Soudan, in Madagascar, in Martinique, in Gaudeloupe, in the Dutch Colonies, in New Guinea, and in the West Indies. On the other hand, it is absent in the East Indies; a number of cases were reported quite recently by Powell from Assam. However, it has also been known a long time in certain subtropical regions, thus in Sicily and Sardinia; however, it is almost entirely absent in the other Mediterranean countries, especially also in Algiers. The attacks always occur, as is especially emphasized by A. Plehn, in such individuals as have lived for some length of time in a malarial district and who have passed through the attacks of fever. The attack is preceded by a sensation of general malaise, lassitude and loss of appetite. The attack proper, without exception, begins with a violent chill which may last an hour and longer, during which the temperature rises rapidly up to 107.6° F. and which is combined with, or followed by

vomiting of dark green, bilious masses. The patients are frightened, restless, sometimes slightly unconscious, tormented by titillation and numbness in the fingers and toes. At the same time they suffer severe pains or a dull pressure in the renal region. The urine at the onset is bright red, of a bloody color, but then during the following discharges, it becomes constantly darker, of the color of old Malaga wine, or it even becomes deep black like coffee. At the same time the conjunctivæ and the skin become discolored to a deep citron or lemon-yellow color. The duration of the attack may extend from six hours to three days. The termination of the attack is not characterized by the sensation of euphoria which usually sets in after an attack of malaria has passed. On the contrary, the patients usually feel very miserable and recuperate slowly. The urine, which forms a profuse sediment containing mucus, epithelia, casts, and detritus, usually shows no blood corpuscles but only dissolved hemoglobin, which can be easily demonstrated by the spectroscope. The number of the red blood corpuscles is considerably decreased as is also the hemoglobin contents of the blood, which may be reduced to 40 per cent. even to 20 per cent. In severe cases the disease leads to death due to cardiac weakness or to subsequent nephritis.

This peculiar clinical picture was considered by most physicians to be a particularly dangerous form of fever. Yersin in 1895 reported to the Société de Biologie that he found a special bacillus in the urine which, however, was recognized by Bréaudat as the bacterium coli. F. Plehn soon afterward found during the attack in Kamerun, either in the blood corpuscles or between them, freely movable corpuscles which did not stain with methylene blue, and pronounced them as the generators of blackwater fever. Other observers, thus Boisson and Kopke, found genuine malarial parasites, others failed to do so. Tomaselli, and after him Ughetti and Galvagno, expressed the opinion that these attacks of fever were produced by quinin, that they were nothing else, therefore, but manifestations of quinin poisoning. The occurrence of hemoglobinuria after the use of quinin had already been observed by several Greek physicians, Brettas, Papabasiliu and Karamitzas. Especially the latter has investigated this question most minutely. Thus he reported at the Medical Society of Athens that a young student by the name of Petimezas, who suffered greatly from fever when young and who had taken considerable quantities of quinin which was kept as a house remedy, one day had an attack of febrile hematuria following the taking of quinin, the same attacks recurred from this time on always after quinin had been taken, both after internal administrations of quinin tannate and also after quinin inunctions. After having no attack of fever for two years he declared his willingness, when enjoying the best of health, to have experiments made upon him, and he actually again had the same typical attacks as formerly after 0.15 and 0.30 quinin sulphate. Karamitzas was able, therefore, to furnish the experimental proof that quinin sulphate even in small doses is capable of producing "hemospherinuria."

The occurrence of hemospherinuric bilious paludal fever was known in Greece as early as the year 1842, when Mauroyannis, and especially since 1858 and 1860, when Antonidas directed the attention of Greek physicians to the same. Coryllos and Karamitzas declared this fever to be a special form of ma-

laria, which attacked especially individuals in marshy districts and particularly those who had passed through several attacks of fever but preferably those who suffered from malarial cachexia, in consequence of refrigerations. The Greek physicians believed concurrently that these fevers were produced by the miasma of the swamps, and not by the quinin, especially because persons who had never taken quinin became affected by it, for attacks occurred after the cessation of the use of quinin and because the same people who, in subsequent attacks of hemispherinuria, had used quinin, had seen the disease disappear (Pampukis).

The opinions of physicians of other nations who had an opportunity to study hemoglobinuric fevers were divided. Most of them considered them to be an especially severe form of malaria and treated them with very large doses of quinin, 8 to 12 grams on the first day (Steudel and Küchel), whereas others considered them as belonging etiologically to malaria, yet they rejected every variety of quinin medication because they noted a remarkably severe course of the disease after the use of the same (Plehn). This was the condition of the question when Koch had an opportunity to see and to study such cases in East Africa. Only after the careful microscopical examination of the blood was he fully in a position to decide as to the malarial nature of these attacks. The most exhaustive investigations led Koch to these important conclusions:

1. That malarial parasites are frequently absent in blackwater fever.
2. That if they are present, their number is in no proportion at all to the hemoglobinuria as should be the case in analogy to Texas fever of cattle.
3. That there exists malaria with very numerous parasites (60 per cent. to 80 per cent. of the blood corpuscles attacked) without resulting in hemoglobinuria.
4. That quite essential clinical differences result from a careful comparison of an attack of malaria with one of blackwater fever (in that in tropical malaria the attack commences at most with slight chilliness, whereas in blackwater fever it commences with a very marked chill, and that the curve in the latter falls much earlier and much more rapidly than in the former).
5. That blackwater fever may combine with two entirely different forms of malaria, with the ordinary tertian fever and with the tropical malaria.

Koch, by numerous observations, has ascertained as positive and beyond doubt that blackwater fever in the tropics, the same as in Sicily and Greece, may be produced by quinin, quite independently of malaria at that. Koch does not believe at all that every case of blackwater fever in the tropics is bound to be called forth by quinin. On the contrary, he acknowledges expressly that "undoubtedly also in the tropics cases may occur which, the same as in moderate climates, may arise in consequence of marked over-exertions and of sudden refrigerations." It does not appear to him "as by no means impossible that insolation may have exactly the same effect." But, "at any rate, quinin plays, in the tropics, at present, by far the most important part in originating blackwater fever." As to the origin of the disease, it requires, according to Koch, a special predisposition which develops gradually in the tropics. It was repeatedly noted that the urine, a long time before the appearance of the attack of blackwater fever, presented a conspicuously dark

color, and also that slight jaundice became manifest. This is explained in that at first only a fraction of the red blood corpuscles is inclined to disintegration and destruction by the quinin. In this case the activity of the liver suffices to overcome the hemoglobin and to transform it into bile pigment, causing hypercholia, jaundice and a dark color of the urine. The excretion of the hemoglobin by the kidneys does not set in until many red blood corpuscles have changed their composition. True hemoglobinuria does not take place until, as Ponfick has found, the amount of liberated hemoglobin is more than one-sixtieth of the quantity present in the entire blood. Fisch recently called attention to the fact that blackwater fever without black urine may arise after the administration of quinin. The chill, in such cases, sets in typically, but the urine is not typically discolored; it shows an abnormal gray or pink shade.

On the other hand, the chill may be entirely absent and yet the urine may present the characteristic appearance, the exquisitely hemoglobinuric discoloration, as was emphasized by Pampukis. That the dose of the quinin taken influences the severity of the attack is explained by Koch in that, with a small dose, only those blood corpuscles are destroyed which are most markedly changed, whereas large doses destroy also the less altered blood corpuscles. Those cases in which quinin acts repeatedly upon the blood and only the first time produces a marked hemoglobinuria, whereas it is well borne on the following days, can be explained, according to Koch, in that the first dose destroys the predisposed blood corpuscles present and that the subsequent doses no longer encounter blood corpuscles that may be attacked. Thus it might be explained that Steudel, Küchel, and others, were able to administer repeated large doses of quinin without doing any harm in patients with blackwater fever and could cure malaria.

The manner in which the predisposition to blackwater fever is brought about is still an enigma, according to Koch. He believes it probable that the climate, in conjunction with previous attacks of tropical malaria, primarily at least, exerts its predisposing influence upon the blood corpuscles. That tropical or subtropical climates do not necessarily play the rôle of causative factor in the occurrence of the peculiar predisposition is shown in a case of blackwater fever in quartana reported by Otto, which arose in our northern latitudes. A patient who, in July, 1901, became infected in Cracow and who became affected in Hamburg by quartan fever, was attacked, when a large dose (0.5 grams) of quinin was administered to him for the first time after an existence of the disease of four weeks, which could not be influenced by any effective therapy, by a typical hemoglobinuria commencing with a violent chill, in immediate connection with this quinin administration.

The views of Koch regarding the origin of blackwater fever were by no means immediately accepted by the physicians of the tropics, in spite of the great number of observed cases reported by him. These physicians have emphasized again and again in particular that such attacks occur also without the use of any quinin whatever. But, as explained in the above, this is by no means denied by Koch. Attacks of febrile hemoglobinuria certainly occur also without quinin. As an unobjectionable witness in this case even old Hippocrates may be quoted, who has reported three cases in which the patients

“μέλανκ ούρησεν.” However, in the greatest majority of cases, it is quinin which produces the attack, as has been unquestionably proven by Koch, for all who mean to consider the question without prejudice.

Koch, by reason of the etiology discovered by him, has established the following laws regarding the treatment of blackwater fever: If a careful and repeated examination of the blood for malarial parasites has shown that the patient does not suffer from malaria, symptomatic treatment is sufficient. The nausea must be combated by proper remedies; especially should plenty of liquid food, milk and mineral waters, be administered in order to dilute the hemoglobin and to prevent the formation of the dangerous hemoglobin infarcts in the kidney. Kohlstock has recommended, in marked dyspnea, the inhalation of compressed oxygen, a measure which was already successfully employed by Baccelli and which rendered good service also to F. Plehn. In combating the anemia which is sometimes enormous, transfusions of blood should, according to the precedence of Steuder, be resorted to.

If malarial parasites are found, the attack may be allowed to pass and then small doses of quinin should be carefully given again. Fisch advises giving 0.2 quinin three times daily, and to increase the daily number of these small doses until the fifteenth day, when seven times 0.2 quinin should be taken. Then the increase should be continued or the same number of administrations persisted in.

However, this is not devoid of danger as even small doses of quinin (thus 0.15 grams in the case of the Greek student) may be capable, later, again, of producing an attack.

Pampukis, by reason of experiments made with Solon Chomatianos on four persons, advises as a substitute for quinin, chinconin, as the latter the same as its sulphate, did not produce an attack, even in doses of two grams. Unfortunately, its efficacy is a very doubtful one, as was shown by the experiments he made with this substance in Blidah.

Quinin hydrobromate was also well borne internally in a dose of 0.8 and subcutaneously up to 0.3; an attack did not occur until injections of 0.37 had been made. As Ferguson claims to have obtained such brilliant results with quinin bihydrobromate in subcutaneous injections of 0.18, this method of treatment of blackwater fever should also be tried.

Future experience will show whether euquinin, which is highly recommended by Celli, may be employed without danger in malarial patients that are predisposed to blackwater fever. The same is true of basicin, a combination easily soluble in water, of quinin and **caffein** which has been successfully employed by Goldmann in several daily doses of 0.5 grams in combination with profuse inunctions of basicin oil (basicin 5.0, chloroform 37.5, alcohol 12.5, fine olive oil 45.0), in patients who suffered from obstinate intermittent fever and who had been unsuccessfully treated with other remedies.

As stated above, all substitutes of quinin are of very doubtful value. Arsenic has been definitely disposed of. Phenocollum hydrochloricum which was recommended by Dieulafoy has met with varying criticisms; Ziemann found it without effect in Africa.

Doubtful are also the results obtained with preparations of eucalyptus, the tincture and the oil, with tinctura helianthi, recommended by Kosatschkoff,

with pombotano bark of Mexico, with cuprein and methyl-cuprein made by Grimaux and Arnaud from quina cuprea, with quinaethylin, with antipyrin, with sodium cacodylate, etc.

Gautier has lately highly praised arrhenal, monomethyl-dinatrium-arsenate which, injected subcutaneously in doses of 0.05 to 0.1, exceptionally of 0.15, is reported to have cured obstinate quotidian fevers which resisted large doses of quinin and even pernicious cases; one or two, rarely three, injections are said to have been sufficient. It is stated that the injections were well borne, the appetite of the patient did not suffer and the destruction of the red blood corpuscles was avoided. Should these extremely favorable statements be confirmed, arrhenal deserves the palm above all malarial remedies, even above quinin. However, it would be highly remarkable if arsenic in this form should display such an intense action against the malarial parasite which it does not possess acknowledgedly if given in other forms.

In the therapy of malaria only one substitute of quinin has attained a secure position, although not equal to quinin, yet next in value to it—that is methylene blue. Taking advantage of the great ease with which the malarial parasite is stained with methylene blue, Ehrlich and Guttman were the first to experiment with the curative effects of this drug, and successfully at that. The dose employed fluctuates between 0.5 and 1 gram and may be given for some time without injury. The urine becomes dark blue after the drug has been taken; a very disagreeable strangury becomes manifest very often, which is best combated by the simultaneous administration of a tip of a knife full of powdered nutmeg. However, besides numerous favorable reports regarding this preparation, unfavorable ones have also been made in that the remedy, regarding rapidity and certainty of its action, does not by any means compare favorably with quinin. In all cases, therefore, in which quinin can be employed, this should be preferred and methylene blue should only be used in those cases in which quinin is contraindicated, for instance, in blackwater fever. Koch has successfully employed methylene blue med. Höchst (1 gram daily) in such cases.

The treatment is really disposed of with the correct administration of quinin, affecting the cause of the disease, according to the ancient principle: *Cessante causa, cessat effectus*.

After quinin has done its duty, the numerous and various clinical symptoms which may be presented by the patient usually disappear spontaneously after longer or shorter periods of time, according to whether the lesions caused by the parasites are severe or slight. The change which takes place in the condition and appearance of the patient is frequently actually wonderful and justifies the designation “Divinum remedium” which has been given to quinin.

However, the conditions of the patients and the severity of many conditions, especially pain, may cause the physician to interfere.

It is an old rule to have the patient stay in bed during the attack. The chill is frequently so severe that the entire bed shakes. A warm bed acts very beneficially upon the patient and also the administration of warm drinks, unless there is vomiting, and also rubbing of the skin with warm woollen cloths has a favorable effect.

If the temperature is very high, ice poultices upon the head, eventually a tepid bath, may act beneficially.

Passionate hydrotherapeutists, especially Winternitz and his disciples, have even attempted to abort and cure the stage of the fever of malaria by the application of cold packs, cold baths, cold douches, with subsequent rubbing. The efficacy of this hydrotherapy is denied by others. That slight infections may be improved or may be cured by them is doubted by none in view of the frequent spontaneous recoveries. Many physicians practising in the tropics, thus the brothers Plehn, consider it directly dangerous in severe tropical fevers to expose the patient to the effects of cold water. As an attack may eventually be produced in such patients by a simple drenching, for instance, a fall into the water, these hydrotherapeutic measures which unquestionably do not influence the cause of the fever, the parasites, should be employed with great caution during the disease itself. In convalescence, however, they may be most extensively applied.

Severe vomiting may sometimes be successfully combated by the administration of cracked ice and opium pills; application of strong irritants upon the gastric region, mustard plasters, mustard poultices, spirits of mustard, also prove to be efficacious. Violent cardialgia and pains in the spleen are alleviated by small doses of morphin, phenacetin, salipyrin, antipyrin and its derivatives, dimethyl-amido-antipyrin, which was brought upon the market as pyramidon by the Höchster Farbwerken, and also the neutral and the acid and pyramidon camphorate and the salicylate in doses of 0.5 to 1 gram, act favorably upon the headache and the manifold nervous phenomena, pains in the limbs, sensation of oppression, without, however, naturally, influencing the morbid process itself. Potassium bromid and chloral hydrate have proven efficacious in case of nervous unrest and insomnia.

The various manifestations of pernicious malaria, threatening as they may appear, do not in themselves require medical interference as they disappear with the action of quinin. Only the dangerous symptoms of cardiac weakness demand the energetic employment of excitants. Subcutaneous injection of ether, camphor oil, musk and, internally, alcoholic drinks, champagne, brandy, strong coffee, etc. Besides, a symptomatic treatment affecting the various prominent symptoms may, of course, be resorted to in that attempts are made to combat the cerebral phenomena, by ice bags, cold ablutions, local withdrawal of blood; bronchitis and pneumonic symptoms by the administration of expectorants; the choleraic manifestations, by the infusion of tannin solutions and by opiates; the colliquative sweats, by atropin.

The severe sequelae of malaria, the so-called malarial cachexia, are very difficult to remove; however, gradually, they also give way to quinin. Naturally, a roborant diet must aid. It is necessary, above all, that the patient be removed from the tropical climate. Change of climate, sojourn in the mountains or upon the sea do not in themselves, as Koch has recently particularly emphasized, cure malaria, but the convalescence of the patient naturally progresses more rapidly in a cooler climate, with careful nursing in a sanatorium, than if he remains exposed still further to the effects of tropical climate. The treatment of the convalescents from malaria does not otherwise present anything particular. The functions of the stomach must be watched

and eventually stimulated by amara, improved by the administration of hydrochloric acid; digestion will also be regulated; constipation is to be removed with mild laxatives or washing of the colon. As the patients are more or less anemic, the usual iron preparations should be given.

The administration of small doses of arsenic in the form of Fowler's solution, or of the waters of Levico and Roncegno to stimulate metabolism is considered indicated by many physicians in such patients.

The splenic tumor which sometimes remains after the attacks and which does not give way even to quinin therapy is sometimes particularly obstinate, especially when connected with the relaxation of the suspensory ligaments of the spleen. A great variety of remedies has been recommended to rid the patient of this very troublesome sequel; local application of Priessnitz poultices and ice, of the electric current, of the constant as well as the induction current (Botkin), quinin injection (Fazio), of injections of Fowler's solution (Mosler), of ergotin and ergotinine (Messerer, Bracassio and Solaro), of carbolic acid, strychnine, even in fact of simple sterilized water (Murri and Boari) into the organ itself. Finally, the radical remedy, the removal of the splenic tumor by means of the knife, has been successfully employed in a great number of cases, thus, in five cases of Jonnesco. The movable spleen has been removed by various surgeons, Rydygier, Zykow, Bardenheuer, or fixed in its position by splenopexia.

PROPHYLAXIS OF MALARIA.

We owe the enormous advances made during the last decades, in the successful combat against the murderous infectious diseases, essentially to the discovery of their generators and to the scientific investigations of their biology.

So soon as the question: Where does the propagation of the generators take place and how are they disseminated from these areas of propagation, has been answered, the measures to combat them are, so to say, self evident. These two questions form the cardinal points around which the problem rotates, the combat against malaria.

As we have explicitly described in the chapter on the etiology of malarial diseases, they are produced by three parasites which are similar to each other yet must be distinctly differentiated from one another and which multiply in the blood of man and especially in the red blood corpuscles but, besides, also in the bodies of certain mosquitoes—the anopheles. The primary locality of propagation of the parasites is in the blood of man; the anopheles obtain from this source the germs which subsequently continue to develop in them and multiply there. Of fundamental importance in the prophylaxis is the answer to the question:

Is man the only carrier of parasites, is the blood of an affected patient the only point of propagation of the same?

It requires very extensive investigations to answer this question with a decisive yes or no. It was necessary to examine all animals living about man, especially in malarial districts, to find whether their blood contained para-

sites in the blood corpuscles; further, whether the parasites which were eventually found were identical with the malarial parasite of man.

This laborious task was assiduously undertaken by investigators of all countries and has led to very surprising results.

Parasites of blood corpuscles were occasionally found in very numerous species of animals of all classes of the animal kingdom, especially in malarial districts.

However, these parasites mostly turned out to be morphologically different from those of man, thus, especially the parasites discovered in the blood of numerous species of reptiles and birds; others again showed unmistakable similarities and analogies of development. Dionisi, for instance, found in bats, three kinds of parasites which could be compared with the three varieties of parasites occurring in man. Poiars found such parasites in monkeys in Goa, Koch in East Africa. The occurrence of typical intermittent affections in malarial districts, in cattle, horses and dogs, which was formerly maintained by many to exist, and is even believed by some at the present time, found a certain support by the discovery of blood corpuscle parasites in these animals. Kolle discovered parasites in cattle in South Africa, Ziemann in Kamerun, in a dog which was attacked by fever of a tertian type; Kuhn claimed to have found plasmodia also in horses which suffered from so-called horse-death.

However, closer investigation of all these blood parasites showed that they did not at all conform to those of man. They could be transmitted with the blood only upon the same species, or at most, upon closely related ones. Attempts to transmit this animal parasite to man were frequently made but always without success. The reverse was done still more frequently and transmissions attempted of human parasites upon various kinds of animals; all these experiments proved negative.

It was not possible even to infect monkeys, with which various investigators, Richard, Di Mattei, Fischer, Bein, Angelini, have experimented. The same negative results were obtained also by Koch, in his numerous experiments made during this great expedition, upon the most varied species of animals. He furnished, above all, the extremely important experimental proof that even the anthropomorphic apes cannot be artificially affected with human malarial parasites. Three orang-utans, three *hylobates agilis* and a *hylobates syndactylus* remained entirely well in spite of repeated injections of malarial blood taken from patients with tertian and tropical fevers. The fluctuations of temperatures which are so characteristic of malaria never occurred, and it was never possible to demonstrate malarial parasites in them. The brilliant results obtained by Koch in combating malaria in Stephansort, New Guinea, and in which he left entirely out of consideration the participation of any animals whatever in the propagation of the disease, are unambiguously in favor of the theory represented by him and by many other investigators, that the human malarial parasites are able to propagate only in man and in the mosquito. We may, therefore, consider this theory as demonstrated now until the truth of the contrary is given in unobjectionable manner.

Resting upon this basis, we mean now to pursue the method of propagation of the disease still further.

If the malarial parasites multiply only in the body of man and in certain varieties of mosquitoes, it follows that they can be disseminated only when they pass out of the body of man and out of the body of the mosquito into the outside world, then, in some manner, again entering the body of the human being or of the mosquito.

The germs can only pass out of the body of the human being if the blood current is open so that blood exudes. Malarial germs are never excreted, as far as is known, with the normal secretions and excretions of a malarial patient. This could only be the case if they contained blood. What, then, happens to the germs present in the extravascular blood? All investigators who concern themselves with this question state that they tarry a relatively short time. It has been frequently attempted to keep the germs alive for some time in such blood kept under the most varying conditions. Laveran has seen them preserved in the blood for ten and more days in a hollow slide. He was not able to determine that the parasites remained alive for this length of time. Sacharoff attempted to preserve the plasmodia in leeches which he kept on ice in a frozen condition. The animals were thawed out every day and small amounts of blood withdrawn from them by the irritation of the posterior part of the body with a crystal of common salt, the plasmodia showed themselves movable for a week and longer, and the movements were even more energetic than in the blood drawn immediately from a patient. Rosenbach, who repeated these experiments found that the parasites remained alive in this manner for at least forty-eight hours. Ziemann, to study the change of the parasite outside of the human circulation, caused leeches to suck on one patient each with quartan and tertian fevers and on two patients with tropical malaria, then kept the leeches in water that was renewed every day and examined the blood of each on the following and the second following days in stained and unstained preparations. He found that the parasites remained preserved mostly up to twenty-four hours without apparently any morphological change, that a further development within the leech, however, did not take place, but, on the contrary, a degenerative process was noticeable after a certain period of time. The protoplasm was scarcely stainable after forty-eight hours or even after twenty-four hours. It had a transparent appearance in the unstained preparation and the pigment was concentrated in thick masses. The chromatin remained stainable for a longer period than the protoplasm of the parasites. All the tropical parasites were extra-globular after two to three times twenty-four hours. Their chromatin was still stainable after five to eight times twenty-four hours. Ziemann did not state, in these transmission experiments, how long the parasites remained alive.

Bein caused leeches to suck the blood of malarial patients, then caught them in tepid water, cut them rapidly and injected the blood thus obtained in quantities of 2 cc. either subcutaneously or intravenously; he obtained a positive result in 4 cases. However, he states that it is advisable not to leave the blood over a certain period (four to five hours) in the leeches as otherwise the movements of the plasmodia become much more indifferent and the parasites die very soon. These statements agree well with the observations of Schoo in Krommenie, who, according to a private communication, did not find tertian parasites living longer than eight hours in the leech.

All attempts have failed to cause multiplication of the parasites in artificial substrata of nutrition, even in ascitic fluid with dissolved hemoglobin and in blood with an addition of peptone (Angelini). The allegedly positive cultural experiments of Coronado, in swamp water, with an addition of blood, are absolutely non-demonstrable. We may conclude from all these experiments that malarial parasites reaching the outside world with the blood may remain viable for a brief period of time but are not capable of propagation. The possibility of a determination of the disease by hemorrhagic discharges of malarial patients must be excluded, therefore.

The second method by which the parasites may pass out of the blood of affected human beings is by stinging and by the sucking apparatus of blood-sucking insects. We know that blood-sucking parasites play quite an important rôle in the transmission of numerous infectious diseases, in so far as they are capable of inoculating germs which are present in the blood of an infected individual, and which, after the sucking adhere to their stinging and sucking apparatus, and are conveyed to healthy individuals by a continuation of the process of sucking. Thus, it is possible, for instance, that the trypanosoma of rats are transmitted from diseased individuals to healthy ones by fleas, the trypanosoma of the nagana by the tsetse fly, etc. The possibility was, therefore, at once admissible that the malarial parasites of man could also be transmitted in such a manner by fleas, bedbugs and also by mosquitoes. However, it was not possible as yet to prove such a transmission of the parasites by blood-sucking insects. A direct transmission of the parasites from affected human beings to other healthy individuals is out of question, therefore, in the dissemination of malaria.

As explained above, parasites drawn from the blood of affected individuals by blood-sucking insects are capable of development and of propagation only in the anopheles.

Only the germs multiplying in the body of the anopheles must be considered in the propagation of malaria.

However, the development and propagation of the germs taken by the anopheles into its stomach does not take place under all circumstances, but it is rather dependent upon certain conditions; first, upon the presence of male and female gametes in the blood sucked; further, upon a favorable proportion of mixture of the male and female gametes, to which fact Ruge especially calls attention; finally, above all, upon favorable temperature conditions, the great importance of which, for the maturing of the sporozoites, was pointed out by us previously, in the epidemiology of malaria.

Now the question arises as to the manner of the further dissemination of the matured sporozoites, the dissemination by the sting of the mosquito which harbors mature sporozoites in its salivary gland is proven experimentally. The planting of the stinging and sucking apparatus into the skin of man takes place simultaneously with the discharge of the saliva containing sporozoites into the small wound. The sporozoites enter into the capillary regions of the skin and are then in a medium adequate to them, the blood, in which they multiply further.

The better understanding of the dissemination of the germs by the sting of the mosquito requires the answering of several questions regarding the

biology of these insects. Why do the mosquitoes suck blood? Do they suck blood more than once? How much time elapses after a mosquito has sucked blood until it stings a second time? The mosquitoes generally live on liquids which contain vegetable nutritive substances, especially sugar, in solution. They find these nutritive substances everywhere, in blossoms and fruits of the most various kinds of plants. It is very easy to nourish them artificially especially with sweet fruits, particularly melons, bananas, and water; however, to be propagated, they require a food that is rich in albumin, blood. To develop the ova, the females must suck blood in regular intervals, as was also proven experimentally by Annet, Dutton and Elliot during their malarial expedition to Nigeria. The quantity they ingest is quite considerable. Schoo has determined the same in 12 specimens, the weight of which amounted to between 1.9 to 4.2, on an average 3.0 mgs. It fluctuated between 1.4 and 2.9 mgs. and was on an average 2.2 mgs. The digestion of this quantity of blood takes place more slowly or more rapidly according to the temperature. With a regular supply of blood on alternating days, the female commences to deposit ova eight days after the development of the chrysalis, and continues to do so every second or third day, if water is at her disposal, till death. One single fecundation by the male is sufficient for a considerable period of production of ova. Annett has kept anopheles alive and productive for at least seven weeks in captivity in cages, and he believes that they probably live still longer under natural conditions. Accordingly, an anopheles female which becomes infected with the first sucking is capable of infecting numerous human beings in the subsequent acts of sucking.

Exact experimental investigations are lacking as to how long the sporozoites remain alive and capable of infection in the salivary glands. Ruge examined the crescent germs of the German proteosoma found by Frosch in sparrows in the neighborhood of Berlin, in Weissensee, in infected gnats forty-five days after their infection. He found them actively motile in some, living, therefore; immotile in others, therefore dead. He says: "It appears accordingly that only a few of the crescent germs will keep alive longer than one month and a half in the salivary glands of the gnats." He concluded, from the great increase in the number of infected sparrows from February to April, that these animals were freshly infected by hibernated culex females which required blood to develop their ova fecundated already in the previous year. It could not be a question of relapses in these fresh proteosoma affections because one attack of proteosoma confers immunity. He says: "We must assume, therefore, that a part of the crescents of the proteosoma hibernate," i. e., in the salivary glands of the culices.

There are no direct observations regarding the sporozoites of human malaria.

Up to this time only reports exist regarding the findings of infected anopheles. Martirano noted that the infection of the anopheles commenced in May, 1900, reached its maximum in October, extended toward the middle of March, 1901, then disappeared not to recommence until June. There can be no doubt, according to this observation of Martirano, regarding the hibernation of the crescent germs of the anopheles, at least for some years. Schoo found infected salivary glands in the anopheles only during summer, never

in those that hibernated in dwellings. He believes that he is able to state with certainty that hibernated anopheles cause the first attacks of fever in spring. The positive proof that the sporozoites in the anopheles perish after a certain length of time and especially that they do not survive until spring in the salivary glands of the hibernating female, is still lacking.

The answer to the question: What becomes of the sporozoites after their carriers have perished? is also of the greatest importance. It might be, *a priori*, conceivable that these germs remain capable of life for some length of time in the water into which the dead mosquito has dropped, or that they may be preserved in the soil, especially during that period of the year in which the development of the anopheles pauses. It would be conceivable that the germs, entering the body with the water or with the dust, produce infections, or, also, that the breeds of the anopheles become infected with these germs in the respective water and grow to mosquitoes that are capable of infection. The numerous experiments which many investigators, and especially Celli, have made with a number of persons, causing them to drink water from a malarial district, never led to a malarial infection. The negative result of these experiments caused the denial of an infection per os. Nevertheless, the possibility of an infection by infected water has continually been pointed out by various authors, and, in fact, these numerous drinking experiments are not absolutely demonstrative. There are always doubts whether the waters coming from malarial districts and employed for drinking experiments actually contained malarial germs. Such experiments would only be conclusive if large numbers of persons would drink of water to which, in the first place, blood from malarial patients containing parasites, and secondly mature sporozoites from the salivary glands of infected mosquitoes, were directly added. To carry out such experiments would not present any difficulties.

It is true, Grassi and Schaudinn have determined that the sporozoites of human malaria are exceedingly perishable structures which rapidly disintegrate, perish in water as well as in fluids which are suitable for their development, such as serum containing blood corpuscles. It appears that the placentic germs of the proteosomes are less susceptible than those of malaria. Actively motile crescent germs of the German proteosoma in the experiments of Ruge showed themselves quite resistant even to transitory injuries. "They were still motile if they were dried at 37° C. after remaining in this condition and being floated again five minutes afterward. They even withstood a brief drying at 60° C. nor did the addition of a $\frac{1}{2}$ per cent. solution of formalin influence their motility, and only in a mixture of glycerin was an immediate arrest accomplished."

It would be desirable at any rate to carry out analogous and extensive experiments with the malarial sporozoites also, so as to be enabled to answer the question with a decisive No as to whether the germs multiplying in the anopheles are capable of disseminating in the media surrounding them and of remaining infective and of re-entering the bodies of human beings in some manner or other.

We may assume, until the very doubtful possibility of the different disseminations by the sporozoites in the surrounding media, water, soil, air,

can be proven, that the sporozoites are disseminated only and alone by the sting of mosquitoes. The sequence of infection is a very brief and simple one accordingly: Man, mosquito, man. Without man affected by malaria there are no infected anopheles and without infected anopheles that sting there are no newly attacked human beings. The surroundings of man should be considered regarding the dissemination of malaria only in so far as it very materially influences the development of the anopheles and the parasites in the latter.

The following possibilities result from the combat with the disease:

1. To destroy the malarial parasite in the infected human beings, thus preventing the anopheles from becoming infected from infected human beings.
2. To protect the healthy from the bites of infecting anopheles.
3. To prevent the development of the anopheles themselves.
4. To retard the development of the parasites in healthy individuals bitten by infected anopheles.
5. To render the healthy unsusceptible to the malarial parasites, that is to render them immune to malaria.

All these methods have been applied in practice.

The first method is recommended by Koch and by Grassi; the second method is employed in practice by numerous Italian investigators, especially Celli; the third has been attempted for a long time by a great number of physicians in the tropics; the fourth is defended by different authors, above all, by Kerschbaumer, as the most efficacious and the most rational; the fifth, finally, would be of great practical importance if it could be successfully adopted.

Wherever the epidemics of malaria are interrupted by periods of freedom from the disease, in the temperate zones by winter, in many tropical regions, as for instance, at the Senegal, by the hot dry period during midsummer, the anopheles, the transmitters of malaria, are absent during these periods. Therefore, no fresh infections occur during these seasons. It is true there are sick individuals but they suffer from the consequences of an infection that has taken place previously during the malarial season, therefore from relapses.

If it were possible to free all patients of their parasites during the period in which no anopheles exist the latter upon their reappearance would find no germs with which to infect themselves and the disease would disappear. Chief attention, therefore, should be directed to locating, during a malaria-free period, those persons who are the hosts of parasites and to rid them of these. During the malaria season proper, however, and in those regions of the tropics in which malaria prevails constantly during the entire year, endeavors must be made to rid all patients of their parasites. But it is not sufficient, according to Koch, to treat only those that show symptoms, but it is necessary to also find those persons that are apparently well but who, nevertheless, harbor parasites, particularly those forms suitable for further development in the anopheles, the gametes; these are the so-called *latent cases*, and particular attention must be paid to them. The proof furnished by Koch, that in many localities in the tropics in which malaria is endemic *the affection is one particularly of children*, and that the infection is disseminated exclusively by small children who are not obviously sick but who harbor in their blood

numerous gametes, spheres and crescents, is one of the greatest achievements in the study of malaria.

The knowledge that children are particularly often affected by malaria is very ancient; this fact was emphasized even by Celsus, and Griesinger laid especial stress upon it. *However, that children are exclusively the carriers of the parasites in many districts in which malaria is endemic and that only the examination of children will determine whether endemic malaria is present in a locality, is a new observation of Koch which is of great importance in the prophylaxis of the disease.*

By the aid of this method, which therefore consisted in finding by systematic blood examinations such persons as were infected by malarial parasites, Koch succeeded, except in a few isolated instances, in permanently ridding them of their parasites by quinin. This was accomplished within a few months in Stephansort, New Guinea, one of the most notoriously malarial districts in the world. The disappearance of malaria from North Germany in the last thirty years is ascribed by Koch to the energetic employment of quinin and the resultant destruction of the malarial parasite in man.

Numerous objections to the method of preventing malaria, as extolled and emphatically defended by Koch, have been raised especially by Celli, Schoo, and Plehn, principally on account of unsatisfactory practical results. Experience shows that many fevers are so obstinate that relapses are persistent in spite of a long continued treatment by quinin. It is impossible, therefore, to rid all hosts of their parasites during the pre-epidemic period. Further, no method exists for determining whether or not the patient is actually cured. It is impossible, for this reason, to state how long the quinin treatment should be continued. The method is questioned because of the relapses which occur after a very long period, the "recidive a scadenza lunga." Besides, it is practically impossible for a physician to discover all the latent cases in a malarial district, and, further, to enforce treatment upon those that are detected. A. Plehn, in reference to the employment of the method in the tropics, emphasizes the fact that the natives do not take quinin and that it is practically impossible to employ the method in the millions of natives that are distributed over extensive areas in order to protect the few Europeans who are present in these districts.

The most serious objection, however, which has been raised to Koch's method of combating the disease, according to the investigations of Marchiafava and especially of Gualdi and Martirano was this, that the sexual forms of the tropical fevers, the crescents, could not be caused to disappear from the blood even by the long-continued use of massive doses of quinin, and that, further, the subsequent development of these forms in the stomach of the mosquito could not be prevented by quinin treatment. Gualdi and Martirano have administered large doses of quinin to patients that had crescents and, after having satisfied themselves, by an examination of the urine, that the quinin had been actually absorbed, they caused numerous anopheles that had been reared in the laboratory to suck the blood of these patients. A considerable percentage of these anopheles were found to be infected a few days later, i. e., on being examined, they contained the characteristic capsules in their stomachs.

It is true, the above-named authors did not follow the development of the parasites up to the formation of the sporozoites in the salivary glands; this is a gap that should be filled up by further investigation. According to the apparently unobjectionable experiments, there can be no doubt that the crescents are neither destroyed by quinin nor are they prevented from further development in the stomach of the anopheles. There results from this fact quite an essential difficulty in the prophylaxis against tropical malaria. The corresponding conditions in tertian and quartan fevers were not investigated by the Italians, but those in the tertian fevers were examined by Schoo in Holland. Schoo arrived at quite opposite results in this variety of the disease. Large numbers of anopheles that had sucked the blood of a patient with tertian fever were without exception found infected. After the patient had taken 1 gram of quinin sulphate for three days Schoo caused 16 anopheles to bite him. An examination of twelve days, during which the anopheles were kept at a temperature of 25° C., showed that none of the mosquitoes were infected. Another patient stung by 10 anopheles during the afebrile period, then four hours before the expected attack having 1 gram of quinin sulphate administered to him in solution, six hours later was again stung by 9 anopheles. All the anopheles were kept at a temperature of 25° C. for twelve days. Of the first series, those prior to the administration of quinin, 8 were found infected, but none of the second series, after the administration of quinin. Schoo concludes from his experiments that in tertian fever not only the asexual forms are destroyed by quinin, but also the gametes and that a single dose of quinin is sufficient to prevent the development of gametes in the mosquito. An investigation regarding the conduct of the quartan parasite after the administration of quinin is still lacking. The characteristic investigations of Schoo, as well as those of Gualdi and Martirano, the repetition of which is absolutely necessary, are in entire accord with the assumption of Koch, that, in Germany, in which country tertian fever is almost exclusively present, this disease has been almost entirely extinguished, by an energetic quinin treatment carried on for a long period of time. It may be expected, therefore, that this form may also, by following the directions of Koch, be extinguished in the tropical and subtropical districts in which it occurs quite frequently, as is well known. However, following the method proposed by Koch is by no means so unpromising even for the tropical form of malaria as it might appear from the above statements. It is a fact determined by many investigators, that the sexual forms of the parasites occur in the blood of the patients only after a number of attacks. Schaudinn found gametes as early as during the first attack in tertian fever in a new infection. But in the tropical form it is about eight to ten days until the crescents appear. Gualdi and Martirano, upon the basis of many experiments, have determined the important fact that, if quinin is given at once during the first attack of fever, the crescents do not make their appearance in the blood. Therefore, it would be of importance to treat malarial patients as early as possible to prevent the development of the dangerous crescents entirely, thus preventing their becoming a source of infection for the anopheles. As in diphtheria, those cases furnish the best and most rapid results which are treated as early as possible, before the formation of larger amounts of

toxin, with the specific serum, so it appears also, therefore, in malaria that those cases present the best prospects of rapid and complete cure which come under treatment with the specifically acting quinin as early as possible, before the formation of the sexual gametes.

It will be necessary, further, to guard the carriers of crescents as much as possible against the stings of the anopheles. Koch did not take such precautions in Stephansort. He found, with the aid of systematic blood examinations, all the patients in the plantation, which contained about 700 people, and placed them under regular quinin treatment. The result was that a steady decrease in the number of affections took place from January to April, whereas usually the disease increased during this period. Two months later the number of carriers of parasites was only a small one. It was exclusively a question of relapses of quartan fever, no longer of tropical malaria. He had succeeded, therefore, in curing those that suffered from tropical malaria, who constituted the majority of the patients. His results, therefore, are in opposition to the defective ones obtained by the Italian investigators, especially by Celli. The manner and administration of the quinin may possibly be the cause of the difference of the results. The plentiful administration of quinin is not sufficient alone to arrive at satisfactory results. It depends, above all, upon how the drug is given. According to Koch, the best method to prevent relapses is this, that in intervals of from seven to eight days 1 gram of quinin should be given, or, still better, in intervals of nine days 1.5 grams should be administered on each of two successive days, and best about 6 A.M., if possible in solution, and that, further, this after-treatment should be continued for at least two months. Celli, in his experiments to prevent the relapses of malaria in the pre-epidemic period, administered daily 1.5 grams during the first four days, 1 gram during the following four days, and 0.5 gram during the subsequent fifteen days.

Schoo made the following experiments with his patients in Holland:

First series: Twenty-five persons affected received 5 grams of quinin in four days and nothing after that. Result: Fifteen relapses from the twelfth to the fortieth day after the last dose.

Second series: Twenty-five persons were similarly treated, but after fourteen days they received early in the morning 0.5 gram of quinin in solution. Result: Nine relapses from the eighteenth to the twenty-second day after the last dose.

Third series: Twenty-two persons were treated as above during the first four days, then, on the tenth and eleventh, on the twentieth and twenty-first, thirtieth and thirty-first, fortieth and forty-first, fiftieth and fifty-first, sixtieth and sixty-first, days, 0.5 gram in the morning. Result: Three relapses on the twenty-fourth, thirty-second, and forty-sixth days after the last dose.

According to this method, he treated his patients in 1901. At present he administers 0.5 gram of quinin every tenth and eleventh days for one hundred and fifty days. To three persons he gave 0.5 gram of quinin for one hundred and fifty days every ninth or tenth day; one of them had a relapse. To another series he administered (he does not state the number of persons) 1 gram every ninth and tenth day, and he also noted only one relapse among them.

The method of Celli, as well as that of Schoo, is different, therefore, from that tried and proposed by Koch. The experiments of Schoo show very distinctly that his results became the better the more he approached Koch's directions. It is not quite apparent why neither Celli nor Schoo employed the scheme tested by Koch. These investigators were in a position to render an opinion regarding the value of the entire method, if they had only followed exactly the directions as given. They should the more especially have done so as Koch has laid very particular stress upon the method of administration of the quinin in his mode of treatment.

Although Celli, Schoo, A. Plehn, and others, do not mean to acknowledge the general decisive significance of Koch's method to exterminate malaria, yet they all admit its efficacy in certain cases, for instance, in a restricted and isolated locality in which the entire population can be controlled, examined and treated, and in which also the new arrivals can be subjected to an examination. This, however, admits that the method in itself is efficacious. Koch never entertained any doubt that great difficulties would be encountered in practice in carrying it into effect, and that it would not be possible to free, at one attempt, every malarial district of malaria. This necessitates, in the first place, the education of medical assistants, quite especially for the blood examinations with the microscope; this requirement can be satisfied only in the course of time; but, furthermore, it assumes a far-reaching influence of the physician upon the population to induce the latter to submit to blood examinations and to the quinin treatment. However, these practical difficulties do not by any means invalidate the principle of this method.

Koch's method of exterminating malaria by the destruction of the parasites in affected individuals is the most rational. Therefore, the fundamental part in the struggle against malaria will in the future be played by this method.

Naturally, it by no means excludes the other methods proposed and already employed in practice; but these, as Koch strikingly explains, belong to the so-called inferior means.

The latter include all endeavors to protect the healthy in malarial districts from the stings of infected anopheles.

A great number of substances exist which if applied to exposed parts of the skin will keep mosquitoes at a distance, especially many very volatile substances, essences, ethereal oils, which answer this purpose. Fermi and Lumbau studied experimentally about 400 culicifuges and found among them only a few which rendered good service for several hours (one to two hours in the house and one-half to one hour in the open air). These are allyl sulphid, eucalyptus oil, cumin oil, cajeput oil, and oil of bitter almonds in a watery or oily solution, or in vaselin, or lanolin.

In experiments which I have undertaken with a number of ethereal oils and carbohydrates I found lemon oil to be the best means of preventing the mosquitoes from biting. It is true, the mosquitoes approach the area of the skin covered with this oil, but they never settle down and, naturally, they do not bite. I convinced myself of this by experiments on a number of persons who were thus uniformly protected. The odor of lemon oil is a very agreeable one; inunctions with the same are not followed by a disagreeable im-

pression, therefore, it may temporarily render good service. I am not able to tell whether, upon long-continued application, it acts detrimentally upon the body, especially upon the kidneys. The old belief that eating of lemons prevents malaria may be due to the excretion of small quantities of this oil through the skin. Di Mattei who, by order of the administration of the railroads of Sicily, experimented for three months with the internal employment of lemon juice upon 137 men and 55 women, renders a favorable opinion regarding the effect. Only a few of those who took lemon juice regularly, one coffee-spoonful in the morning before breakfast, became affected, whereas the larger number of those who were attacked by fever were those who did not follow the cure regularly. Those who had not taken any lemon juice at all showed by far the greatest number of affections. Di Mattei ascribes the preventive action of lemon juice to the fact that the skin of those who employed this remedy permanently became permeated with the peculiar odor which, as a rule, we are not able to detect, but which drives away the mosquitoes.

The ancient belief that those who eat garlic and whose exhalations have the characteristic odor of allium oil are not bitten by mosquitoes, was proven to be well founded by the investigations of Fermi and Lumbau, as allyl sulphid, the oil of garlic, was experimentally shown to be one of the best culicifuges. It is true, the unbearable odor of this substance opposes the general application of this remedy.

Other endeavors were directed at driving the mosquitoes at least out of living-rooms and bedrooms and at keeping them out of these. Quite a number of substances drive away the mosquitoes, thus any form of smoke, especially tobacco smoke, formaldehyd, iodoform, fumes of oil of turpentine, menthol, nutmeg, camphor, garlic. But these remedies do not all destroy the mosquitoes in the dwelling rooms. The mosquitoes hide in the remotest corners under the furniture, beds, etc., and are not injured. Chlorin alone is capable, under such conditions, of killing the mosquitoes. To obtain rest during the night, pastils are often burned in the dwellings. The best remedy was found to be chrysanthemum powder, "Zampironi" pastils made of chrysanthemum and potassium nitrate, further, "Zanzolina," a mixture of chrysanthemum, valerian and larvicide, recommended by Celli. Kerschbaumer recommends, as zanzolina distributes coal particles in the air, the following formula:

R	Pulv. flor. occlus. Chrysanth. ciner. variaefol. dalm.	} āā 4 parts.
	Pulv. rad. Valerianae officin.,	
	Pulv. Kal. nitr.....	
M.	Exactissime. D. ad vitrum epist. vitr. claus.	

He gives the following method of application:

"The remedy should be ignited—in a room of 30 to 40 cubic metres 3 Zampironi or a tablespoonful of powder—toward sunset with the windows open. The mosquitoes are aroused at once and most of them escape from the room. As soon as one-half of the pastil is burnt, the windows should be closed rapidly and not opened again until the following morning. Un-

necessary opening of the door should be avoided. Any one wishing to do more may burn the entire dose at the open window and, after closing the latter, a second reduced dose." It is absolutely wrong, according to Kerschbaumer, to fumigate only with the windows closed and then, during the swarm-time of the mosquitoes, to ventilate for hours. Kerschbaumer believes the effect of the chrysanthemum smoke becomes manifest in that it is extremely repulsive to the mosquitoes and suppresses the blood hunger in them. Accordingly, they attempt to escape and, if they do not succeed, they remain motionless in a corner of the fumigated room as long as the faintest trace of odor is perceptible to them but not any longer to the olfactory organ of man. However, as soon as the smoke has escaped from the room, and the atmosphere again clears, those mosquitoes that have remained in the room and were not killed emerge again and attack persons who sleep in the room. There can be no question, therefore, of a reliable protection by means of these fumigations.

Much more rational and effective are undoubtedly the measures aiming at keeping the mosquitoes away from human beings by mechanical preventives. The habit of protecting ourselves from the bites of mosquitoes during the night by mosquito nets is ancient. The employment of the latter is quite general in the tropics. The beds are completely surrounded by gauze, the meshes of which are so small that the mosquitoes cannot slip through. However, if there is a small hole in the material or if the net is insecurely fastened, the mosquitoes are sure to find this spot and the protection becomes worthless. If a part of the body is immediately adjacent, the mosquitoes sting through the net. Therefore, even this protection is an uncertain one and depends upon many factors.

The idea of covering all windows and openings of a house with mosquito netting, instead of merely protecting the beds with it, was a great stride forward in rendering dwellings free from mosquitoes. This has been most energetically introduced into practice by Grassi and Celli. In the dangerous fever districts of Italy, in which the railroad employees are on duty not only during daytime but also at night, during the swarming time of the anopheles, these men suffer exceedingly from malaria. Celli undertook the task of rendering some of the dwellings in a few, especially dangerous districts, of Latium, mosquito-proof. All the doors were supplied with some kind of an outer door (see Figs. 15 and 16) the sides of which consisted of screens that were too closely woven to allow the anopheles to pass through the meshes. Exact experiments have shown that the distance between the individual wires must be such as to have 11 wires in 2 cm. (Fig. 17). Naturally, the outer doors were made self-closing. Likewise, all windows, chimney openings, sinks, in short all avenues to the interior of the house, were also closed with screens. Besides, Celli had all the inner walls of the house painted white so that every mosquito, which had, after all, entered, might at once be recognized upon the white surface. The employees who left the house between sunset and sunrise were instructed, furthermore, to protect their hands by gloves and their heads by mosquito nets. The results accomplished by these arrangements must be called actually brilliant ones, according to the reports regarding them. Whereas these employees who lived in unprotected

houses and who had not taken any precautions for their personal protection from the mosquitoes, then as before, became affected by malaria to 60, 80, and even 100 per cent., those that were protected were exempt or nearly so. When cases of the disease did occur among the protected persons, it could be demonstrated that errors had been made in the protective measures, that is to say, that these persons, because they did not believe in the protection or because the measures were too troublesome to them, had availed themselves of the prescribed arrangements but carelessly or not at all.

At first, many smiled at the preventives. However, when they saw that those who conscientiously carried them out remained healthy and free from

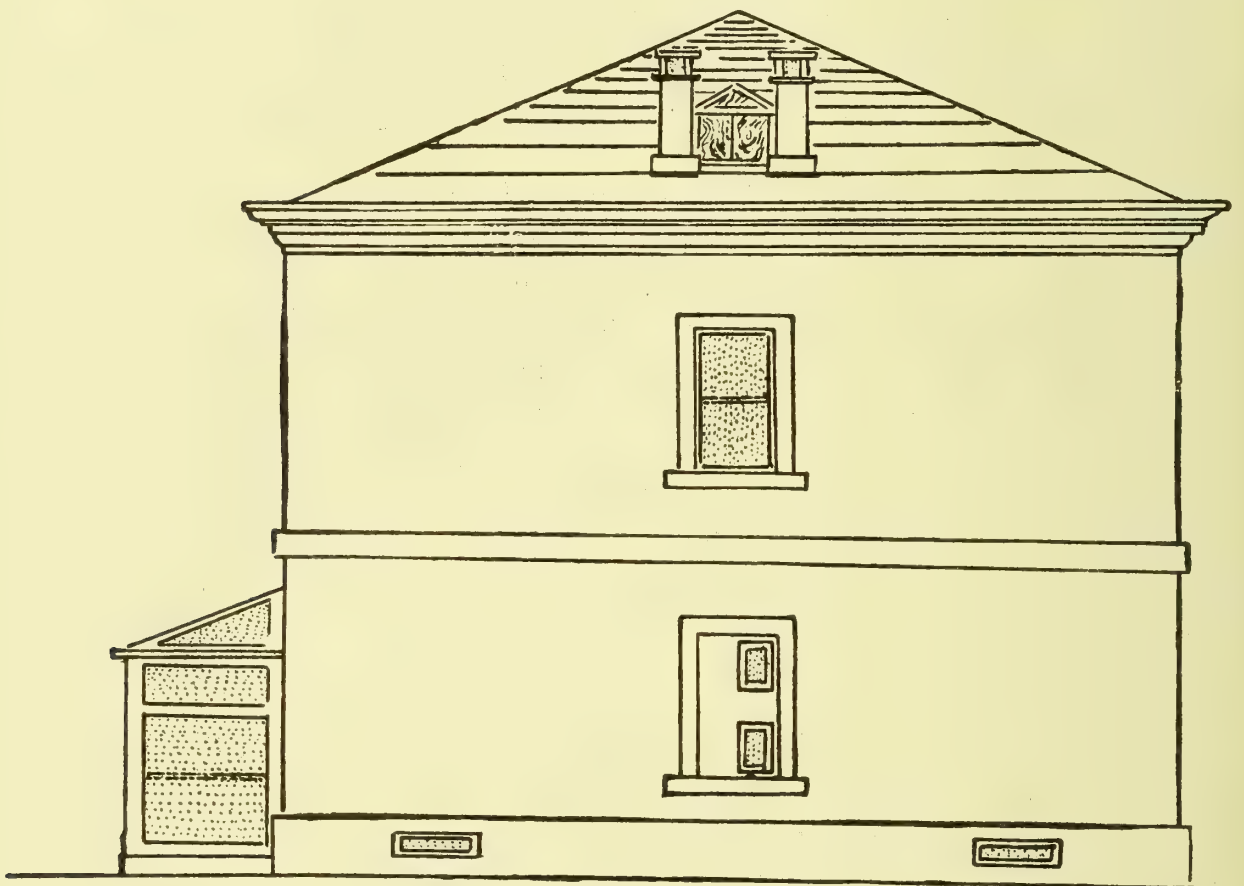


FIG. 15.

malaria, their opinion suddenly changed. The favorable results obtained, especially in Latium, are the reason why this manner of prophylaxis is now introduced in many other parts of Italy. The pleasure of enjoying the refreshing evening air on porches protected by metal screens and an undisturbed rest in sleeping-rooms that are free from mosquitoes should be sufficient reason for the adoption of the prophylaxis, by means of metal screens, more and more in districts that are infested by mosquitoes. According to the reports of Daniels, there exists a variety of anopheles throughout all Central Africa, which is much smaller than the other forms, the anopheles funestus; therefore, to render the prophylaxis by means of screens effective in these districts, it would be necessary to select much narrower meshes of the protecting wire screen than those recommended by Celli and Grassi for Italy.

We shall now discuss the third method of preventing malaria, i. e., the

prevention by means of destruction of the mosquitoes; for no malaria is present in those places in which no anopheles exist. To adopt this method successfully, the biology of the anopheles was studied most minutely. The

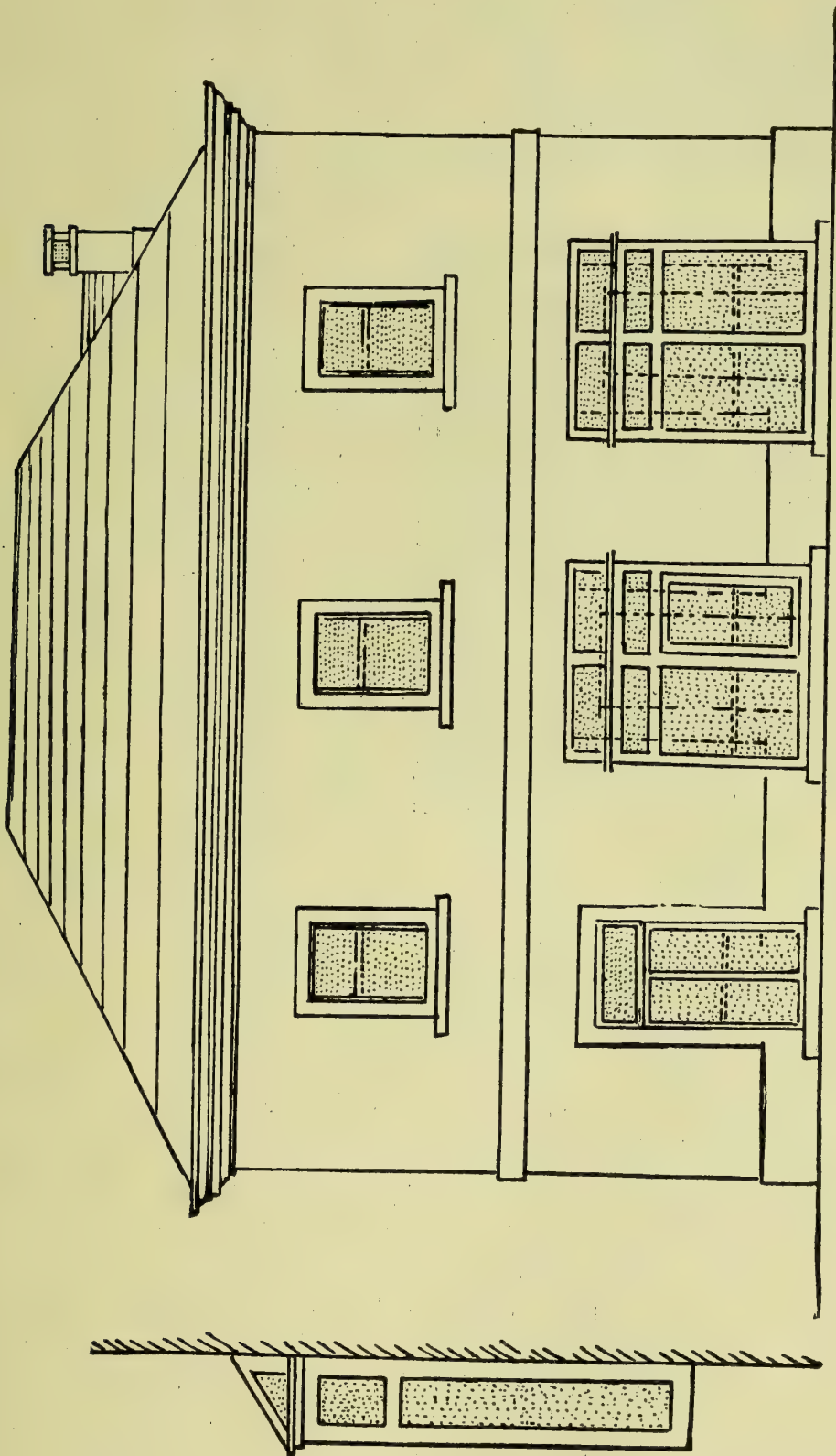


FIG. 16.

opinion of most investigators, Koch, Grassi, Celli, and others, by reason of these studies, is a very pessimistic one in regard to the possibility of eradicating the anopheles. Koch believes such an undertaking to be utterly hopeless, whereas Kerschbaumer, in contrast to the above-named authors,

thinks the problem to be quite feasible. Malaria, according to his opinion, is "only" a "pool fever," and the anopheles are easily exterminated in the pools. The quintessence of his own remarks he summed up in a number of sentences. Mosquitoes do not develop without the constant presence of water; they do not develop in sea-water, nor in brackish water consisting of equal parts of sea-water and fresh water, which, therefore, contains about 1.3 per cent. of common salt. They do not develop in running water because the larvæ are disturbed in breathing and in feeding, because the formation of the imago from the chrysalis is interfered with by the current, because

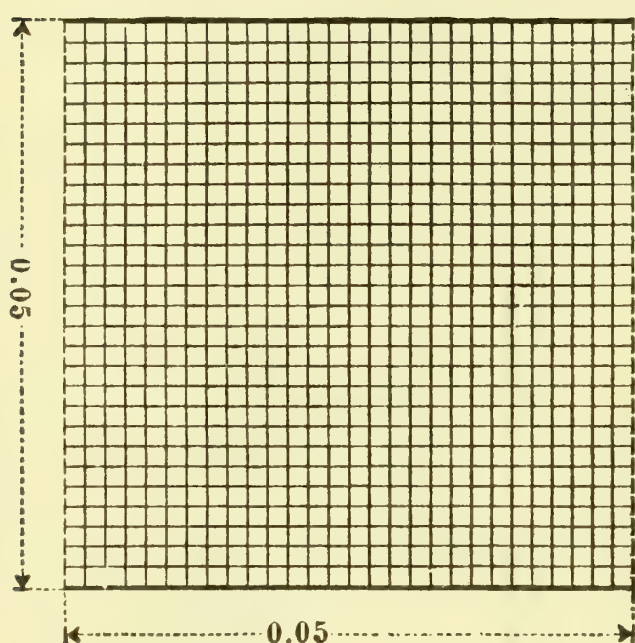


FIG. 17.

the imago requires a quiet water to creep out. Further, they do not develop in stagnating bodies of water with continuously agitated surfaces, nor in almost clean water without scarcely any organic constituents, nor in putrid water, so-called lemna water; in stagnant waters with temperatures of less than 12° C., in bodies of water, lakes, lake ponds, pond lakes, and in ponds, swamps that are deeper than 1 metre on an average; probably because they must at times go down to the bottom to shed their skins and because the active journey from the bottom to the surface would be too colossal a perform-

ance for the larva that is 1 to 3 mm. long and is in the first or second larval stage. Nor do they develop in the shallower shore regions of these bodies of water, because they are exposed to the danger of being seized by the waves and thrown ashore. On the other hand, they develop in small ponds or swamps, in pools. "All neglected natural and artificial, small, smallest, permanent or periodical, accumulations of water (for instance, in cement basins, tubs, stone or wood troughs, barrels, vats, pots, broken pots, etc.) are hydrobiologically small swamp pools." Those that become filled with rain water, Kerschbaumer calls "heaven-pools," those that are filled by groundwater, "ground-pools." The anopheles develop, according to Kerschbaumer, in the so-called dinobryon pools, i. e., pools with clear, healthy water, rich in zooplankton, the chief form of which is the genus dinobryon of the flagella protozoa, and only when these are not available do they go wherever the culex pipiens breed, especially also into the muddy, discolored, stagnant chroococcaceæ waters that are poor in animal organisms, but not into the putrid lemna waters rich in decomposing matter. It follows from the statements of Kerschbaumer, that the anopheles may develop almost anywhere in the neighborhood of human habitations, in all possible vessels and hollows in which fresh water accumulates and stays for some time. We shall leave it undecided whether or not the statement is correct that anopheles cannot

develop in bodies of water that are deeper than 1 metre. At any rate, the important fact that the smallest quantities of water, such as accumulate, for instance, in the points of attachment of the stems of the leaves to the trunk of palms, in hollow stumps of bamboo, empty banana peels, castaway tin cans (Koch), are ample for the development of the anopheles, enables us to understand that the idea of Kerschbaumer, to exterminate the breeds of the anopheles in all pools, especially in the tropics, at once appears to be without any prospect whatever. Nevertheless, such an attempt may under some circumstances be of advantage in restricted localities and the number of mosquitoes decreased. I shall not fail, therefore, to enumerate the remedies tested by Kerschbaumer. Crude oil, 0.5 litre to the square metre of water, was found to be the cheapest "suffocating means," by which the ova, larvæ and chrysalises are cut off from contact with the atmospheric air. Quite as rapidly, in still smaller quantities, does turpentine oil, that is, olive oil and a little turpentine oil (1:10) act. Sapol also appears recommendable. As "poisoning means" he employs chrysanthemum powder, the effect of which, it is true, lasts only twenty-four hours, and "larvicide" introduced by Celli, chemically impure gallol from the chemical works "vormals Weilerter Meer, in Ueberdingen" on the Rhine, which discolors the water to a yellowish-red tinge and which does not permit any growth as long as the yellowish-red color persists. Besides, it appears as though laurel and rosemary, although they do not injure full-grown larvæ, yet are surely fatal to smaller ones, and are serviceable in keeping ditches free from larvæ of mosquitoes. Attempts were also made to prevent the development of the anopheles in pools of water by mixing fresh water with sea-water in such a proportion as to obtain contents of salt which cannot be borne by the anopheles. Naturally, such measures can only be adopted at the seacoast, for instance, in the canals of the drained marshes in Holland into which sea-water can be introduced by proper pumps. However, agricultural objections, for instance, that the grass does not grow so well with water rich in salt and that the cows are said to give less milk, are opposed to the carrying out of this plan (Schoo).

Finally, Kerschbaumer also advises the "Enttümpelung" (removal of all pools) of a given district by mechanical measures of various kinds, such as permanent flooding, periodical flooding, periodical washing out, digging off, filling up, draining; these measures are also advised by other authorities, and to their extensive practical accomplishment many ascribe the disappearance of malaria from entire districts, especially in North Germany (Grawitz).

For the sake of completeness, it may also be mentioned that, to exterminate the mosquitoes, it has been advised to catch the hibernating females in the cellars, and that it has been proposed in America to raise masses of dragonflies because they feed on mosquitoes.

It appears highly problematical, according to the above-explained conditions for the development of the anopheles, whether it will be possible to exterminate the mosquitoes, and, with them, malaria, by any of these measures. In fact, in all places in which malaria has disappeared, the anopheles are still present as before. It is true, their number may be reduced by such

measures, for the timely destruction of one anopheles larva in spring prevents the development of its offspring which amounts to millions in the course of one summer. There can be no question that the danger of infection may thus be slightly diminished. However, it is certain that the intensity of the infection is by no means always parallel to the number of anopheles present, which is quite conceivable; for only when numerous sources of infection, i. e., many affected persons, are present, will the number of the existing anopheles be of more essential significance to the origin and intensity of the epidemic.

To protect the Europeans in the tropics from malaria, a method has been recommended by various authors which is based upon the fact that the infected anopheles, as is quite natural, are mostly found in the dwellings of the natives. It was proposed, therefore to build the residences of Europeans away from the villages and settlements of the natives, and visits to the settlements of the natives should be avoided as much as possible, especially at night. The resting stations which generally harbor anopheles, and generally such as were infected by former visitors, should not be patronized when expeditions are made along the caravan roads, and expeditions by vessels should anchor at a certain distance from the settlements. As anopheles do not pass over certain distances and as, besides, the peculiar odors exhaled by negroes are said to act really enticingly upon the anopheles, it seems as though the actual danger of infection, with a strict separation of the dwellings of the Europeans from those of the natives, would be materially lessened if they were to pass the nights in the huts of the natives or in the immediate neighborhood of the same. Malarial diseases have already been materially reduced by the local separation of the native quarters from the dwellings of the Europeans in many districts in which the European population had suffered severely from malaria. F. Plehn states: "Batavia, simply by the removal of the dwelling places of the Europeans from the neighborhood of the colored population, has become a healthy city from one that was infested with malaria, long before the gratuitous distribution of quinin among the natives had commenced." The systematic execution of this principle would be advisable, therefore, in all localities in which it could be accomplished.

One of the oldest measures, further, adopted for the protection of those who set out for malarial regions, is the prophylactic administration of quinin. As quinin cures malaria, it was assumed that a quininization of the body would be bound to prevent the development of the disease. Quinin prophylaxis was employed even at a time when nothing was known regarding the animate nature of the infective agent. Laveran reports that the Count of Bonneval, during the siege of Belgrade, in 1717, protected himself and his troops by quinin.

The quinin prophylaxis was most extensively tested by English and French physicians during military expeditions into malarial districts. The opinions are partly favorable, partly unfavorable. The majority of the observers maintained that even small doses, 0.15 to 0.3, taken in regular intervals, afforded quite a marked advantage, in so far as many were protected from the disease, and the pernicious attacks were surely prevented. The quinin prophylaxis was extensively employed in the Civil War in the United States. All physi-

cians were of the same opinion regarding the favorable effect of the practice. To quote but one example, Warren regularly gave to 200 men of his regiment, during the fever season from April to October, 1863, 0.3 gram of quinin sulphate daily. Among these 200 men were only 4 fever patients, whereas the rest of the regiment (about 400 men), that did not take quinin, showed more than 300 cases.

These good results of American physicians were opposed by partly directly unfavorable experiences made by English physicians in various expeditions in tropical malarial districts.

There can be no question that, on the one hand, the severity of the infection, on the other, above all, the method of application of the quinin played a very essential part. After the African explorer, Schweinfurth, and, after him, several other observers, Herz, v. Vivenot, Hayem and Plehn, had in Germany called attention to the quinin prophylaxis, the report of Graeser, published in 1888 in the *Berliner klinische Wochenschrift*, regarding the successful prevention of malaria by quinin, during five voyages in the notorious harbor of Batavia, Tandjong-Priok, created a certain sensation. The entire crew received during the evening of its arrival in Tandjong-Priok 1 gram of quinin each, dissolved in gin. The same dose was repeated on the eighth, twelfth, and sixteenth days after arrival, while 0.5 gram each was given on the tenth and fourteenth days. The result was a noticeable decrease in the number as well as in the intensity of the malarial infections. Graeser reported later, in a supplement, that his successor on board the vessel, Dr. Buwalda, obtained still better results in that he administered quinin even three days before arriving in Tandjong-Priok, and also during the entire stay on the coasts of Sumatra and Java, which lasted five weeks, three times per week 1 gram dissolved in gin to each member of the crew. Only two cases of malaria occurred, in two officers who had not taken any quinin, but not a single well-developed case of malaria among those of the crew who had taken quinin. It is true, a genuine "koarts (fever) epidemic" broke out on the tenth day after the departure from Priok; however, this did not show the character of typical malaria but only rises of temperature to 102.2° F. to 103.1° F., weakness in the knees, and malaise, and had entirely passed off after two to three days without causing any noticeable disturbance in the running of the ship. Graeser, a pupil of Gerhardt and Binz, regarded his experiments as a proof of the views of the animate character of the malarial toxin when it enters the body in malarial districts, encounters its specific antitoxin already present in the body and for that reason ceases to develop.

The discovery of the parasite by Laveran gave a new impetus to the endeavors. Thus, for instance, did Sésary practice quinin prophylaxis very successfully in Algiers. His directions were to take 0.15 to 0.20 of quinin daily with the meals, but no more. He succeeded in keeping entire families healthy for three years in very unsanitary districts. He emphasized, however, that the dose is not sufficient in hotter countries.

Barthelémy, who had 0.10 to 0.20 of quinin administered daily during the campaign in Dahomey, did not observe that any of the men became affected. Quennec, in Madagascar, ordered 0.20 of quinin to be taken daily after landings and the same dose given again in the evening. Although he noted

numerous cases of fever in spite of prophylaxis, he did not see a single case of perniciosa.

It would lead too far to enumerate all cases in which quinin was successfully administered prophylactically. The essential point of the question is always, what dose, and how often is it to be administered, to prevent all affections.

It is certain, as stated above, according to the investigations of Kerner and Prior, that quinin, if taken into a healthy stomach, appears generally as early as during the first half hour in the urine, and that the end of the excretion occurs usually during the last hours of the second, rarely at the beginning of the third, day. It is to be expected, therefore, that the administration on two succeeding days of a certain dose of quinin would be sufficient.

Marchoux, in his experiments at the Senegal, found that 0.25 every second day was not sufficient, and he believed that 0.25 should be taken every day.

Burot and Legrand advised 0.3 to 0.6 every two to three days, Maurel, 0.75 to 1 gram every four to five days; Plehn administered 1 gram every eight days, Zahl even 2 grams, successfully, in Kamerun. However, as such doses, according to the opinion of Plehn, are not tolerated for any length of time, he recommended 0.5 gram every five days, Ziemann 0.5 gram every four days.

Accordingly, the views of the various observers regarding the most efficient method of administering quinin have gradually, by reason of numerous practical experiments, approached each other in that the method of administering larger doses in intervals is preferred to the daily taking of medium doses. Koch, on account of his observations in the most dangerous tropical regions, arrived at the conclusion that the same doses of quinin should be given prophylactically which are necessary to prevent the relapses. He recommended to give at first 1 gram every five days, later 1 gram each every tenth and eleventh days, best in solution. If, nevertheless, fever occurs, the dose should be increased to 1.5 gram and the intervals reduced to one to two days. With a temporary danger of infection, quinin acts most excellently if taken in this manner; it affords "almost certain protection" (Koch). Koch adds: "Unfortunately, however, this remedy, if taken in doses that protect sufficiently, is not tolerated for any length of time in the greatest majority of cases." A marked aversion to the drug becomes manifest, the stomach loses its tolerance so that the affected persons rather take chances of some slight attacks than continue the use of the remedy.

The apprehension that the therapeutic efficacy of quinin would be diminished in those individuals who had taken it as a preventive, did not materialize in any form.

The bad, bitter taste that produces aversion, and the fact that quinin is not well tolerated, especially during the hot season, were the reasons why Celli endeavored to find a combination which could be taken for some length of time without injury and without producing aversion. It appeared to him that the ethyl carbonate of quinin—the so-called "euquinin"—answered this purpose. Experiments showed that this preparation can be taken for

four to five months without injury. Celli then undertook several series of comparative investigations to discover the relapse-preventing effect and, at the same time, the prophylactic action of euquinin, on the one hand, and of its hydrochlorate and bisulphate, on the other hand.

Of 50 persons who had taken 0.25 of the bisulphate every two days up to 0.5 every day, none became affected; of 98 with daily 0.5 of bisulphate, none; of 35 with 0.5 to 1.0 every Saturday, 1; of 25 persons who had taken 1 gram of hydrochlorate five days, 3; of 103 persons who had taken 0.5 to 0.75 to 1.0 of euquinin daily, none; of 42 persons who had taken 0.5 of euquinin daily, none; of 74 persons who had taken 0.25 of euquinin daily, 4; of 64 persons who had taken 0.25 to 0.50 daily, 6; of 138, $10 = 8$ per cent.; whereas 20 per cent. to 66 per cent. of those persons became affected who were not treated and were used as control individuals.

The experiments prove the excellent prophylactic effects of the employed quinin salts. All the salts were surprisingly well tolerated during the longest experimental periods, from July 1st to November 15th, four and one half months, even in the largest doses that were taken daily. It is true, gastric disturbances, quininism and, exceptionally, hemoglobinuria occurred, but the well-being of those treated was excellent, upon the whole. Celli advises, therefore, the same as Koch and others, the prophylactic employment of quinin in malarial districts especially for those who are forced to work at night or before daybreak in the open air.

Euquinin was excellently well tolerated for a long time. However, the high price of the product is against its extensive employment.

Arsenic has been highly praised as a prophylactic. But careful experiments have shown that it does not possess any value as such. Even in combination with quinin and iron it did not prove to be serviceable in the experiments of Celli and Vivinzi.

It is highly important that, in districts infested by malaria, the most effective remedy, quinin, is placed at the disposal of the population in a pure and unadulterated form as well as at a low figure so that the poor are also able to enjoy the blessings of the drug. As formerly, the expensive Peruvian bark was adulterated with all possible ineffective drugs by avaricious dealers, so has also quinin, likewise expensive, been mixed with ineffective substances which only increase its volume and weight. Naturally, a preparation containing 80 per cent. of foreign materials, as has been determined, renders any rational employment futile. It must be acknowledged as a laudable measure, therefore, that Italy, which suffers so much from malaria, has regulated the sale of quinin by law, so that the impecunious in the various infected districts are able to procure a good preparation either gratis or at a low figure. The French Academy of Medicine also, in view of the ravages of malaria in Corsica, declared by means of a report rendered by Laveran, "that the distribution of the most important quinin preparations in all malarial districts of France, Corsica and of the French colonies should be regulated by a special law, permitting even the poorest to obtain quinin of a pure quality anywhere as has already been made possible in Italy."

Finally, mention should also be made of protective inoculations. It has been attempted to utilize the blood serum of animals that enjoy a natural im-

munity to malaria. Celli and Santori injected into a number of individuals up to 130 cc. of blood of buffaloes, cattle and horses which were raised in the Pontine and Maccaresian Marshes, and then inoculated these individuals with malarial blood containing parasites of quartan as well as of estivo-autumnal fever. All the individuals became affected by malaria, but the period of incubation was remarkably prolonged.

A new method of inoculation against malaria has very recently been reported by Kuhn, Staff Surgeon of the Imperial Defence Troop of German Southwest Africa. Kuhn believes he has found a suitable means of combating malaria in the blood serum of horses which have passed through the so-called horse pest in Southwest Africa. Kuhn considers the "horse pest" to be some form of malaria. He found in this disease, with Lübbert's blood corpuscles, parasites which resemble the parasites of tropical malaria of man very much, only, according to the slightly inferior size of the blood corpuscles of the horse, they are a little smaller. These findings are in incompatible contrast to the fact determined by various investigators (Nocard, Theiler) that the virus of horse pest passes through filters that detain bacteria. Horse pest, therefore, cannot be produced by parasites as large as the parasites of malaria. Horse pest and malaria, therefore, are by no means similar diseases, produced by related generators, but two entirely different affections which have nothing else in common than their occurrence in the same districts, one happening in man, the other in the horse. Kuhn maintains that he is able, by the injection of one to several cubic centimetres of "horse pest serum,"

1. To exterminate the existing cases of malaria so that this serum may serve as a substitute for quinin;

2. To destroy all generators present in the body, thus aborting the relapses; and

3. To produce a protection against new infections.

To explain the effect of the serum he has brought out the following theory: The inoculation introduces into the body substances which are equal or very closely related to the protective substances produced by the malarial virus itself. Whereas malaria usually forms only a few protective substances in every attack and terminates only gradually after a great number of attacks, with danger to the life of the patient, the process is accelerated by the supply of protective substances. If, now, the quantity of protective substances introduced with the serum, in combination with the amount formed by the patient in the attack of fever, in the main fever, as Kuhn expresses himself, is sufficiently large, all germs are killed and the patient is cured. However, if the protective substances are not sufficient to exterminate all the germs, these may produce, after some time, two, three, four, five attacks, "subsequent fevers" which, however, cause only moderate symptoms because the amount of protective substances still present is, after all, too great to allow the development of threatening manifestations. The remaining germs are developed during a disturbance of the equilibrium of the body and cause subsequent fevers until they are fully destroyed. Then the patient is permanently "salted" against the fever.

Thus far Kuhn. He maintains that he obtained practically good results

with the serum. Nevertheless, the entire theory arouses well-founded doubts. The fundamentals are wrong upon which the theory is constructed. This consideration notwithstanding, the favorable results observed may actually be present. However, even these appear questionable as the course observed after his serum inoculations is very similar to the course of untreated malaria. For, as we know, malaria often ceases spontaneously and then follow some relapses which also recover spontaneously, or "subsequent fevers," as Kuhn calls them.

Besides, if the treatment of malaria by the serum of horse pest were successful, this would be the first instance that an infectious disease of man could be cured by the serum of an animal suffering from another disease. We must doubt, therefore, until the proof of the contrary is actually furnished, that the new method of Kuhn is of value in the struggle against malaria.

IMMUNITY TO MALARIA

What is the condition of immunity in malaria? Does recovery from the disease confer immunity, as we observe in many other infectious diseases, or not? The general opinion of physicians has always been that one recovery from the disease not only confers no immunity, but, on the contrary, produces a distinct predisposition. The opinions were at variance only in regard to one form of the affection, namely, quartan fever. Old Aetius said: "*Quartana febre idem homo bis neque capitur, neque unquam captus est, nec de caetero capietur, si semel sanus fiat.*" This opinion had remained uncontested and was even confirmed as being absolutely correct by Fernelius. Only Sennert, Hevermann, Casp. Reies, Wier, Madai, and others raised objections to this theory, also Sydenham; the latter, however, maintained that, if a person had once recovered from quartan fever and was, later, attacked a second time by the disease, the second affection would always be slight and would be cured spontaneously after a few attacks. That, however, this favorable prognosis was not always correct was shown later by Marcel, Donat, and others. Probably nobody believes in it to-day. The numerous reports of a continuance of the disease for years, even for decades—as longest duration of the affection Gabelshower gives a period of forty-eight years in one case—point more than anything else against the occurrence of a permanent immunity even in quartan fever.

It was entirely new and surprising, therefore, that Koch, supported by a number of important observations, answered the question: Is there immunity to tropical malaria? with "yes," and he gave the following reasons: He had noted, in conformity with experienced physicians of the tropics, that in patients with tropical malaria, unless they were treated with quinin, the attacks became gradually less and finally ceased. Then followed some groups of attacks until, at last, only a few isolated attacks occurred in which the temperature scarcely rose to 100.4° F. The patients, therefore, enjoy a certain immunity.

It was especially remarkable to Koch that entire groups of the population in many malarial regions of the tropics suffered but little or not at all from malaria. The coast negroes of East Africa are immune, whereas the negroes

of the same race living in the mountains are not. The Indians and Arabs that live on the coast of East Africa are immune, whereas new arrivals are exceedingly susceptible. The Chinese coolies who are newly introduced into Sumatra are severely affected by malaria and frequently succumb to the disease; after they have lived there for some time, they no longer become affected and are, therefore, valued highly.

Koch assumed, by reason of these facts, that these groups of inhabitants had become immune by recovery from malaria, whereas Golgner meant to ascribe the immunity of the adult population of a malarial region to an insusceptibility to malaria existing since birth, to some form of selection of those that are immune. Koch was able, by his studies during his great expedition to Batavia and New Guinea, to furnish the proof that his opinion of the acquired immunity was the correct one.

He found entire villages in malarial districts, for instance, Bogadjim and Bongu, in which the adults were free from malaria, in the best of health, whereas the children were almost all affected by malaria. He often noted among the children weak, emaciated forms, with flabby skin and distended abdomen; in children between three and six years of age he frequently observed splenic tumors which projected beyond the border of the ribs. He determined that, nevertheless, no malaria cachexia developed in them. After the children have passed through the malarial period, they commence to bloom and they develop into well-formed, robust individuals who are no longer harmed by malaria. A condition for the occurrence of this exquisite immunity is, however, that the natural course of the disease during childhood must not be disturbed and interrupted by quinin treatment.

Still another observation of Koch is extremely interesting. He found islands in the Bismarck Archipelago, in which only quartan fever was present. If these people who were immune to quartan fever went to Stephansort, they were there attacked by tropical malaria and by tertian fevers. "One form of malaria, therefore, does not protect from the others."

Now the question suggests itself: Does the European also acquire immunity by recovering from the disease? This appears not to be the case from experiences gathered up to the present, or only in some few individuals.

Koch will not advise anybody to immunize himself in a similar manner.

A. Plehn, who has closely investigated this interesting and important question of immunity, expresses himself in a different sense, by reason of observations made by him in Kamerun.

He examined negroes of various tribes, Duala, Abo, Bassa, Kru, and others, and determined at first, quite in accord with Koch, that the children were greatly affected by malaria, that of

18 children under two years.....	17 = 94 per cent.
26 children between two and five years....	24 = 92 per cent.
40 children between five and ten years	34 = 85 per cent.

had parasites in the blood.

Besides, he found parasites in 26 of 43 (60 per cent.) adults examined. He also was able to determine splenic tumors projecting to three finger-breadths beyond the costal arch in 27 of 38 healthy negroes between the ages

of ten and twenty years, i. e., in 71 per cent., and in 62 of 104 healthy negroes, between the ages of twenty and sixty years, i. e., in 60 per cent. He concluded therefrom that adult negroes also frequently become affected by malaria, that, therefore, they did not enjoy an absolute, but only a relative, immunity, because the attacks were mostly slight and they recovered without quinin.

The disease in children, according to his observations, contrary to the statements of Koch, did not run so mild a course, in spite of the occurrence of numerous parasites in the blood. He concluded, therefore, that children born in malarial districts enjoyed a certain inherited immunity in that they descend from immune parents, and that, therefore, the malarial parasite, if it did attack them, became a "harmless symbion."

However, it unquestionably follows from the case-histories reported by him that the children, after all, suffer from febrile movements from the earliest ages on and that they become affected with splenic tumors, as was observed by Koch in the native children studied by him. If the adult negroes of West Africa, quite in contrast to the observations of Koch in the adults of several other malarial districts, frequently became affected by malaria and suffered from marked splenic tumors and also from anemic conditions, the variations in the occurrence of the immunity must be due to racial differences in the inhabitants of different districts with endemic malaria. Immunity is surely always present, although its degree may be different. A. Plehn believes that the European does not possess hereditary immunity, which causes the disease to be so mild in the negro children, and that, therefore, the attacks run a much severer course in the European than in the native. It is fraught with danger to him, therefore, if he would wish to acquire immunity by passing through numerous attacks. Nevertheless, an artificial immunity may be accomplished even in him, namely, by quinin prophylaxis in smaller doses. Although all more severe attacks are almost entirely obviated by the administration of a dose of 0.5 gm. every five days, slight febrile movements will occur. Individuals treated in this manner would have malarial germs permanently in the blood, it is true, but they would not fall sick and would thus gradually become immunized.

His idea is, therefore, to effect, by small doses of quinin, an artificial attenuation of the virulent parasites in the body and, with the aid of these attenuated parasites, to produce immunity artificially. The future will tell whether it will be possible to obtain practical results with the systematic application of this method. This is not very likely to be the case. The natural process of immunization in children takes place in the course of a number of years. Koch found in Bongu that, of children under two years of age, 100 per cent., between two and five years, 46.1 per cent., and between five and ten years, still 23.5 per cent. were affected with malaria, and only persons over ten years of age were not affected at all. It appears, therefore, that it requires almost a decade to acquire immunity.

Would it be worth while for a European who, after all, remains only temporarily in the tropical malarial districts, to strive for such an artificial immunity with the aid of parasites that are artificially attenuated by quinin? I believe not. And is there even a certain degree of probability that the

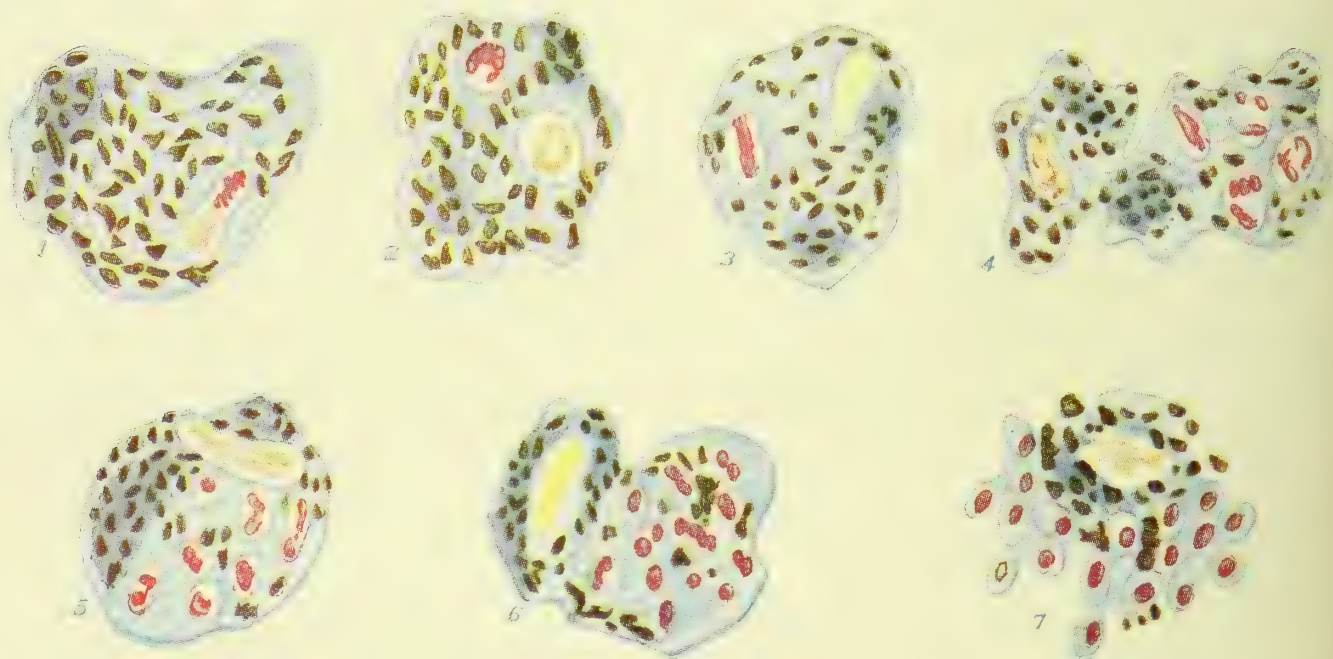
striven-for immunity is actually acquired in this manner? It is scarcely possible to answer this question in a positive sense. Therefore, an essential benefit will not be derived from the idea of Plehn.

The prospects of a practically applicable artificial immunization are at present, in spite of the determination of the fact that immunization is possible in malaria, equal to naught. Naturally, the hope remains that, as in other disease which confer immunity, an artificial method of immunization may also be found here.

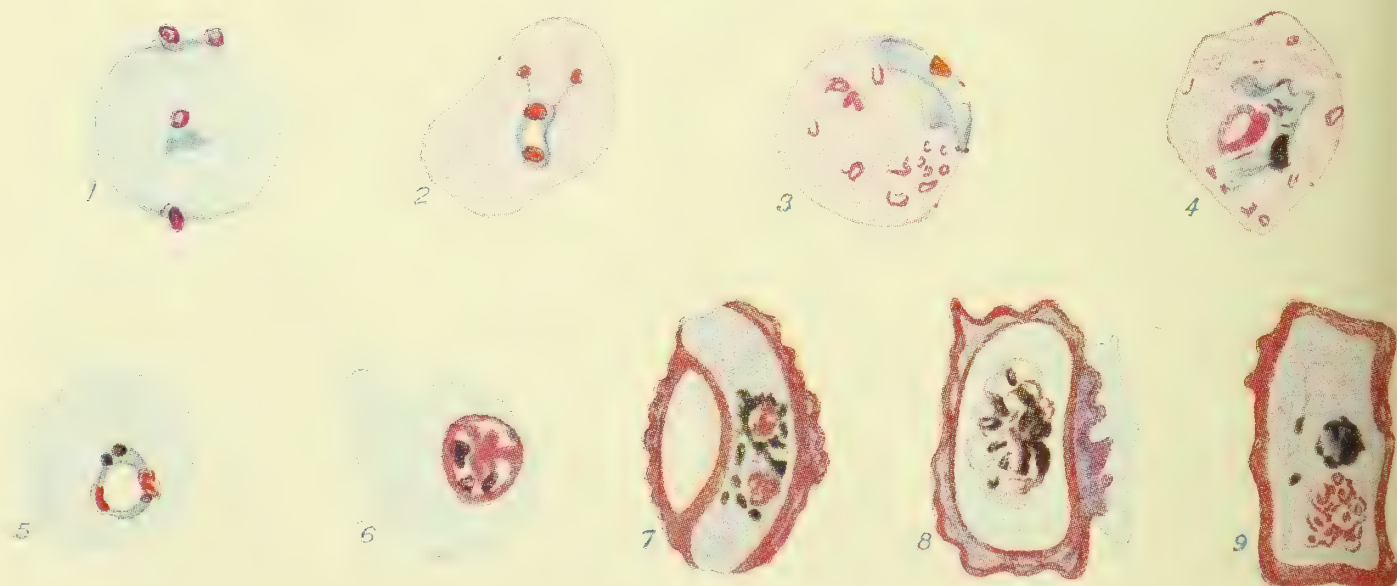
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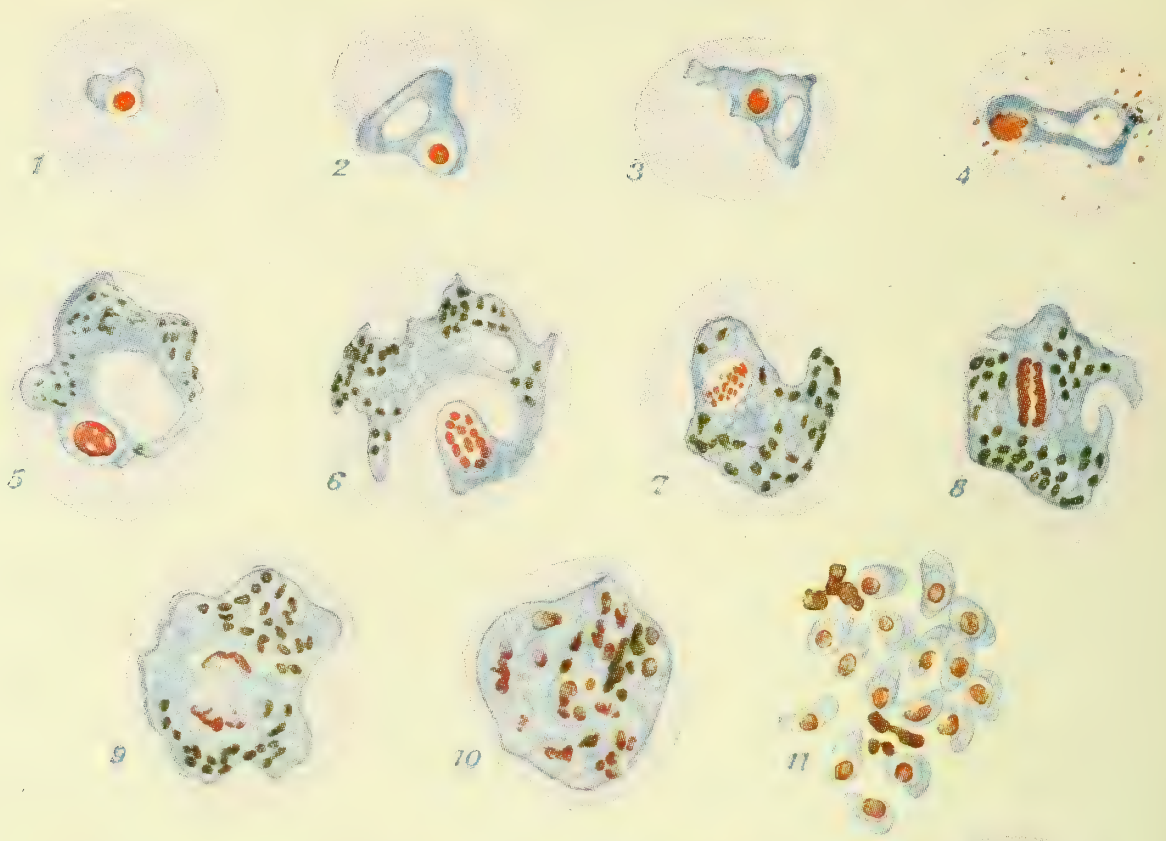
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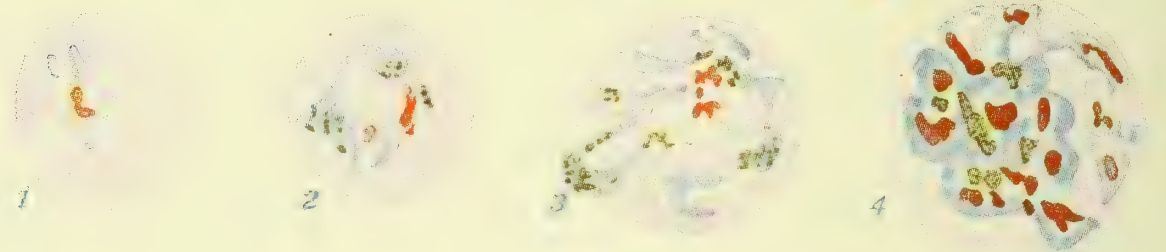
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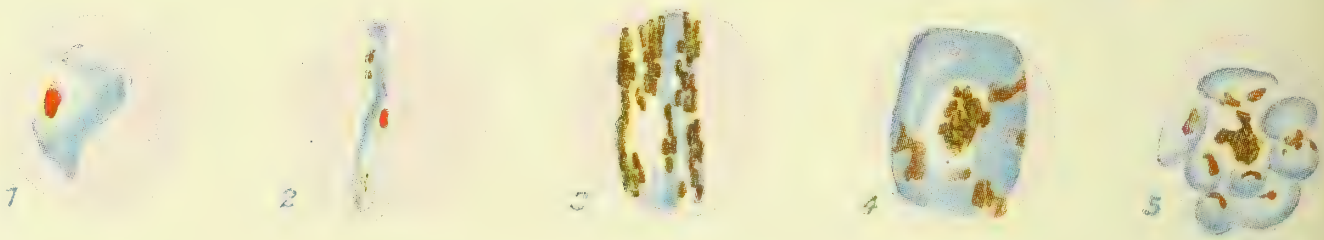
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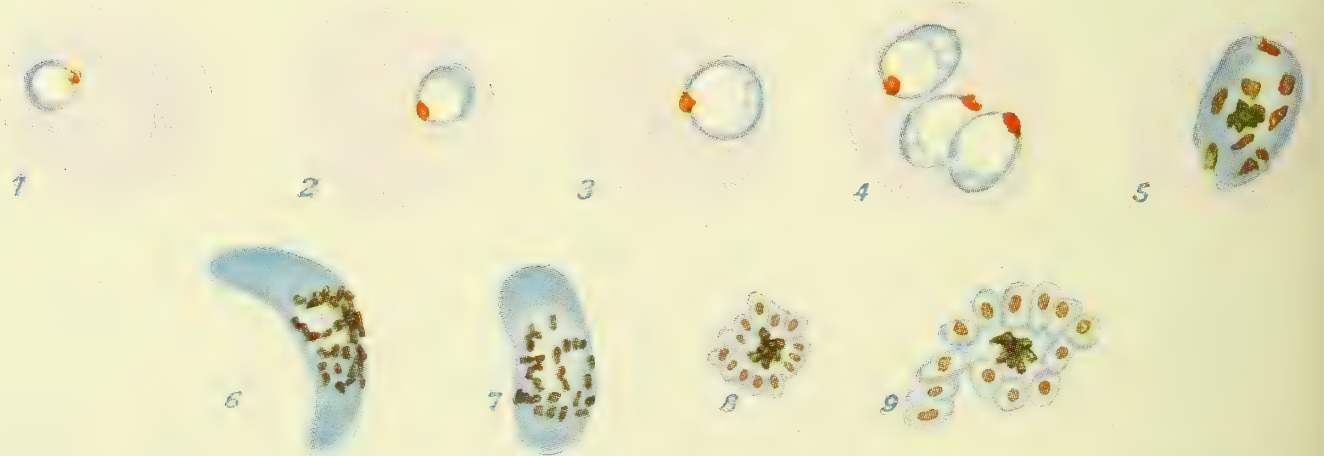
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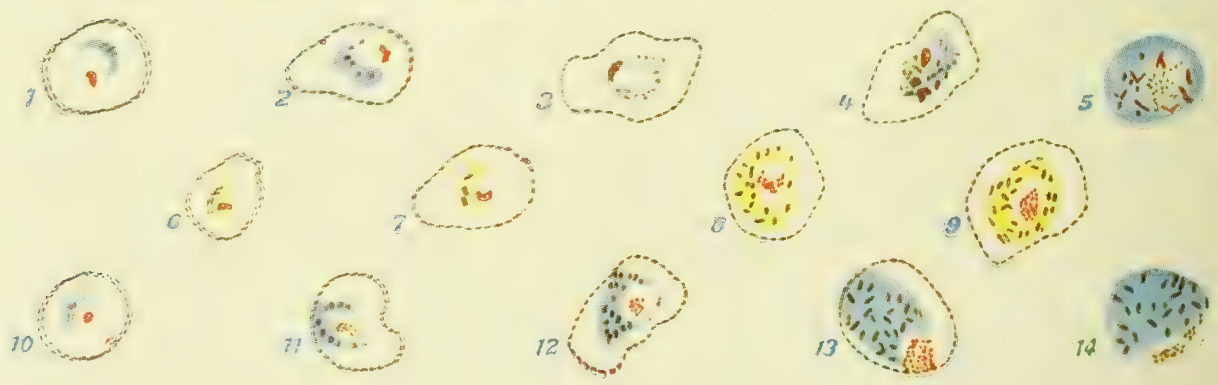
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D



E



EXPLANATION OF THE COLORED PLATES

- A. Development of the tertian parasite (after Schaudinn), staining (after Romanowsky-Nocht), then with iron hematoxylin (after Heidenhain). Enlargement about 2250 to 1.
1. Schizonte shortly after the entrance of the merozoite.
 2. Schizonte about eight hours old.
 3. Schizonte about twelve hours old.
 4. Dotted host cell.
 5. So-called large tertian ring.
 6. Schizonte about twenty-four to thirty-six hours old. Loosening of the nuclear substance.
 7. Schizonte thirty-six hours old. Blending of the chromatin into an equatorial plate.
 8. Segmentation of the equatorial plate into daughter plates.
 9. Separation of the daughter plates.
 10. Multiplication of nuclei to schizogonia.
 11. Accomplished schizogonia.
- B. Morphological changes of different stages of development of the tertian parasite (after Schaudinn). The blood was withdrawn during the height of the attack, after the patient had taken, two and one-half hours previously, one and one-half grams of quinin. The young schizontes, one and two, are stained more pale than normally, obliterated, distorted in shape. The older stages of growth, three and four, torn and stained diffusely. The chromatin is also torn and its parts distributed.
- C. Development of the quartan parasite.
1. Young schizonte.
 - 2 and 3. Schizontes presenting the characteristic ribbon-shape, two about twenty-four hours old, three about forty-eight hours old, with abundant pigment.
 4. Immediately before segmentation.
 5. Consummated schizogonia.
- D. Development of the tropical parasite (after Koch).
1. Small tropical ring.
 2. Medium tropical ring.
 3. Large tropical ring.
 4. Three times infected blood corpuscle.
 5. Schizonte immediately before segmentation. Finger blood.
 6. Crescent.
 7. Oval.
 - 8 and 9. Segmentation forms from the spleen.
- E. Development of the tertian parasite (after Ruge). Enlargement 1000 to 1.
- 1, 2, 3, 4, 5. Development of the schizonte.
 - 6, 7, 8, 9. Development of the microgametocytes.
 - 10, 11, 12, 13, 14. Development of the macrogametes.
- F. 1. Macrogamete.
2. Microgamete.
 3. Formation of microgametes.
 4. Macrogamete fecundated by a microgamete.
 5. Ookinetes from the intestinal contents of the anopheles (after Schaudinn). Enlargement 2250 to 1.
- G. Retro-formation and schizogonia of the macrogamete, forty-eight hours before a relapse occurring after three and one-half months (after Schaudinn). Enlargement 2250 to 1.

MEASLES, MORBILLI, RUBEOLA

By O. HEUBNER, BERLIN

Definition.—By the designation measles, we understand afebrile disease of the upper respiratory mucous membranes and of the general cutaneous coverings, having quite a typical course in its symptoms, belonging to the acute exanthemata, and which is always due to the entrance of a specific poison derived from a previous case of measles.

Etiology.—Although in the descriptions of authors of the middle ages measles cannot be recognized with certainty, it is at least likely that we are dealing with a very ancient disease, perhaps of the same age as variola. The susceptibility of the human race to the poison of measles, in spite of the continuous repeated flooding, has not been attenuated even to-day, for but very few persons, comparatively, fail to have an attack of measles as soon as they come in contact with a patient ill of the disease. Even the fetus in utero by means of the maternal blood may be attacked by measles, and the aged as well are attacked by the disease if they have never been previously exposed to the contagion. This has been noted in members of royal families or inhabitants of islands, in which for decades contagion has not appeared. On the other hand, no one is ever attacked by measles who has not in some manner or other come in contact with a case of measles, in Iceland as well as in Central Africa, i. e., in other words: Only a specific poison developing anew in man is capable of producing the disease.

This poison only develops in man and not outside of the human organism, for in his surroundings it does not usually remain active very long; for even a residence in places in which measles patients have been previously present, a few hours after careful ventilation, confers no danger to susceptible individuals. It may be that the poison, by means of directly infected body linen, utensils, perhaps also, for example, by a letter that has been rapidly closed, may be transported to certain distances inside of a short period of time, in this way bringing about a contagion; but without question this is not possible after a prolonged period. Its increase in the affected organism is very decided, for a single patient is capable of conveying the disease to dozens of susceptible individuals, and by a further development hundreds and thousands of human beings may be infected, as has occurred upon isolated islands (Faroe Islands) twice in one century, the condition having been observed by careful and responsible physicians.

With the exception of individual rare cases which appear to be endowed with a congenital personal immunity against the disease, so that in spite of frequent opportunity of contagion they are never affected, there is but one circumstance which conveys protection from the poison, that is recovery from

the disease. The immunity acquired in this way in most persons is usually permanent, it commonly lasts for the entire life. Unquestionably measles has sometimes occurred several times in the same individual, but this belongs to the greatest rarities and does not vitiate the rule. I remember having seen two attacks of measles (in an interval of several years; relapses are not meant) in a child in which the first attack was only rudimentary. We often hear, in the treatment of a case of measles, that the patient has already had an attack of the disease.

This permanent immunity is all the more remarkable as another immunity artificially acquired, that against diphtheria, in no other acute affection appears to disappear so rapidly as in the case of measles.

The region to which the poison first adheres in the body of the affected individual, how it first distributes itself, in what connection it occurs with the symptoms of the disease, are up to the present still unknown facts. This may be readily explained as we have absolutely no knowledge regarding the origin and nature of the contagion. All endeavors of the best investigators to lift the veil of this secret have remained without result. If we may conclude from other analogies, the primary point of attack of the virus might properly be referred to the upper respiratory mucous membranes. It has not as yet been determined by conclusive experiments, by means of what secretions or excretions of the body the contagious principle is transmitted to the healthy. In the case of measles we usually speak of a fleeting contagion, but observations like those of Grancher do not favor the view of the immediate transmission of pathogenic bacteria from the sick body by means of the air. This investigator, in a ward in his hospital for children, by a process invented by him (wire boxes around every bed) prevented the individual patients from coming into direct personal contact with a measles patient, whereas, naturally, the current of air from one bed to another was not hindered. When a child attacked by measles was brought into the ward at the onset of the period of incubation, it was shown that not the neighboring children were attacked, but a child was affected which was attended by the same nurse as the child that had the attack of measles. This nurse had nothing to do with the other children because both the mentioned ones had been nursed while isolated on account of suffering from another infectious disease (scarlatina). In the usual course of things, naturally, those nearer the measles patient are more threatened than those distant, but even here the transmission occurs more by contact (touch, transmission of infected substances, and the like) than by the air. Naturally, upon close proximity the transmission by means of vaporous particles (in sneezing, coughing and the like) is important.

After reception of the poison by the healthy, a number of days pass before the first symptoms of the disease appear. This time, called the *period of incubation* of the disease, is in most individuals, in the case of measles, a regular period of about eleven days. This was first determined by Parnum on the Faroe Islands where there was frequent opportunity of studying the course in such patients as exposed themselves but a single time to the contagion. The exanthem usually appears exactly upon the fourteenth day after contagion has taken place. Later, when it was possible, by means of taking

the temperature, to note the first onset of the pre-eruptive period, it was shown that the period of incubation in a restricted sense, required the previously mentioned eleven days.

The general susceptibility to contagion shows a certain limitation during the first four or five months of life; but even here there is no absolute immunity. I observed an undoubted attack of measles with very characteristic symptoms, with fever and well-developed eruption in a boy aged fifteen weeks, whose brother and sister, aged respectively three and one and a half years, simultaneously suffered from extraordinarily severe and rapidly fatal attacks of measles; the sister died four days after, and the brother three days after the appearance of the disease in the nursling. In a second case I saw a boy aged twenty weeks attacked by measles, with a very marked and intense eruption, with high fever. In both cases rapid recovery without complications occurred.

After the first year of life the disease is much more frequent, and from the second year on the susceptibility is the same as later in life.

The susceptibility which is quite general, on the one hand, and the immunity acquired by an attack, on the other hand, determine the character of measles as an *epidemic* disease. It is only an apparent disease of childhood, as, almost without exception, in all larger areas of population all individuals have had an attack of measles before they have passed beyond the limits of adolescence. Where measles breaks out in a population in which no immunity has been acquired by previous attacks, as in 1846 upon the Faroe Islands, every one is attacked. Among nearly 8,000 inhabitants upon the island only those old persons were spared who sixty years previously, while they were children, had passed through an attack of measles.

The seasons of the year have only an influence in so far as there is a connection between a general closing of schools and kindergartens, as during vacation, and in other institutions for children. From this concentration of young children, the occasional upflaring of measles in large cities always renews itself if, since the last larger epidemic, a greater number of children who are not yet immune have grown up, so that they find entrance into the previously mentioned institutions, in which there is always recurring opportunity for contagion through some child attacked with measles coming from an infected district of the city. Thus, as Medical Director of a district, I formerly had an opportunity in April, May and June as well as in October and November, to observe marked epidemics of measles. The older children bring measles home from school to the younger members of the family, and where a population, particularly in case of the poor, live close together in the same street, the disease spreads rapidly from one house to another and from floor to floor in the same house, until many children recovering from the malady have become immune to the disease, the locality thereafter showing no cases for several years. The same conditions prevail in smaller cities and villages in the case of all the children in certain districts.

The same phenomenon is noted in the wards of a children's hospital unless it is especially protected. A child is admitted on account of catarrhal affection which is not recognizable as belonging to measles and on the eleventh day an epidemic occurs in the ward, attacking all children that have not been

protected by a previous attack. Here the results are much more serious than in the city, for in the hospital the affection attacks children that are already ill from other causes, producing *secondary* measles, the disease then being far more serious.

PATHOLOGICAL ANATOMY

The anatomical examination of children that have died of measles does not give the slightest clue regarding the nature of the disease. The parts of the body and the organs which during life have shown distinct deviations in form and color as well as in function at the autopsy show no alterations which characteristically differ from catarrhal and inflammatory phenomena in the same parts in a number of other affections. In the skin the dilatation and tense congestion of the small veins and capillary nets of the cutis are recognized, which may be assumed from the clinical symptoms. Along the walls of the smallest veins leukocytes are found arranged in rows, the lymph channels are wider, the skin succulent, and disseminated foci-like collections of round cells are present in many areas of the cutis. The entire inflammatory or vaso-motor change of the skin in measles appears particularly to attack the upper layers nearest the epidermis in which cutaneous vascular nets are present. The hair follicles and sebaceous glands are surrounded by great numbers of capillaries; the infiltration of these structures is probably the cause of the nodular prominences which characterize the eruption of measles.

The catarrhal process in the respiratory mucous membrane perhaps shows anatomically a somewhat greater intensity in that the vascular system of the submucosa is more markedly implicated and the extra-vascular infiltration of the mucous membrane is greater than in ordinary catarrhal processes. This is of especial importance in regard to the course of the catarrh of the ears and of the larynx. When the catarrhal affection enters the finer and finest bronchi there is an early development of interstitial cellular infiltration of the peribronchial and perivascular connective tissue.

Almost always—especially in the severer rapidly fatal cases—(as in many acute infections of infancy) a very decided cellular hyperplasia of the entire lymphatic system develops. All peripheral and internal lymph glands and other conglomerations of adenoid substance such as the pharyngeal and palatine tonsils, the solitary follicles at the root of the tongue, walls of the pharynx, and throughout the entire intestinal tract such as Peyer's patches of the ileum, are found to be in a condition of intense medullary swelling, so that an inexperienced observer not infrequently, especially upon viewing the lower parts of the small intestine, erroneously supposes enteric fever to be present. The acute hyperplasia of the spleen in measles is as a rule less developed.

Whether this marked cell infection of the lymphatic organs which occurs in a few days is in connection with the regular appearance of leukocytosis in measles has not yet been determined with certainty. [In uncomplicated measles leukocytosis does not occur.—Ed.] At all events, in the child, even in cases in which the number of leukocytes is not markedly increased, the blood picture is altered in the manner that the lymphocytes are decidedly

less than the polynuclear leukocytes. Large forms of these, such as mast cells, some authors have met with more frequently in the blood of measles than elsewhere.

The heart occasionally shows implication from the poison of measles, especially the endocardium is not rarely implicated, whereas the pericardium is not so liable to become affected. The myocardium may also occasionally be damaged by the poison.

The vascular twigs and the parenchyma of the kidneys are less frequently damaged than in the case of scarlatina, however, occasionally the renal structure is attacked and then shows conditions that occur in scarlatina.

The pathological alterations of the lungs will be considered in describing the deviations from the normal course of the disease.

CLINICAL PICTURE OF MEASLES

In measles it is practical to differentiate various phases or stages of the clinical course which may be distinctly recognized at the bedside.

After the stage of incubation which was explained above, the *catarrhal stage* follows, this is succeeded by the *eruptive stage*, and this, again, by the *period of convalescence*. The catarrhal stage is also designated as the stage of invasion, and, formerly, the name prodromal stage was given to it. The stage of eruption is spoken of as the stage of bloom or florition.

These individual periods often find a very characteristic expression in the picture of the temperature curve. Thus, in one of the following charts, that of a boy aged twenty-one months, the fever, which accompanied the mucous membrane affection in the catarrhal stage, showed a curve of three days with two remissions; from the fourth to the seventh day a continued fever followed during which the exanthem appeared over the entire body, and after complete development of a cutaneous eruption the temperature fell in a critical manner, entering upon the stage of convalescence. (Compare the two following temperature curves, Figs. 18 and 19.)

The character of the fever—remittent in the first days, highest and most continued during the development of the eruption and falling rapidly after the complete development of the eruption—is noted in all typical cases of the disease and, even in regard to decisive exacerbation and remission in the various phases of the course as well as in regard to the absolute height of the fever, the greatest variations occur. That there is a connection between the highest temperature and the greatest intensity of the eruption, as was previously mentioned, can only be decided with certainty by one who has observed a great number of cases, as well in regard to the eruption as to the continued temperature course. This has not been carried out by any one as yet; and it scarcely appears to be of practical importance. But it is important to note whether or not the characteristic course of measles is shown; to observe this through the most manifold variations is hardly difficult to the trained clinical eye; to deny it means to disregard a well established fact in a very careless manner. I am of the firm opinion that some day the discovery of the poison of measles will clear up the clinical type of the affection in the same fortunate manner as in the case of malaria.

In connection with the fever we will first describe the regular course of the affection.

The *period of incubation* of measles is usually free from symptoms, deviation from this rule will be described later on.

The onset of the disease is but little characterized and differs only slightly from an ordinary bronchitis. In daily practice the chronology of the whole course is much more difficult to determine than in the case of scarlatina or

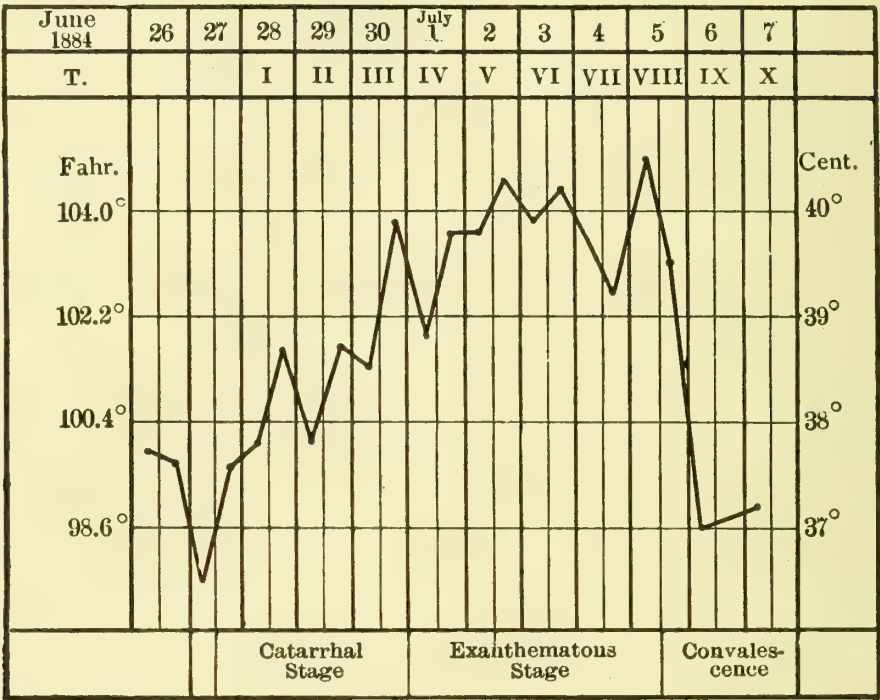


FIG. 18.

even diphtheria, because the parents are not able to say exactly when the “coryza” began. Only where—in a previous illness—the temperature of the child has been taken from the beginning of the disease (as in charts 18 and 19) is the rise in temperature above the normal noted from the onset (early in the morning in the rectum above 99.5° F., in the evening over 100.5° F.), even though the child very often shows no distinct subjective disturbances in its general condition.

In cases where this is absent there is no reason, even for very anxious parents, to send for a physician. This only occurs upon the appearance of an exanthem and thus it happens that the practitioner often enough does not have an opportunity of observing the first or the catarrhal stage of measles; and even in cases in which he takes regular records of temperature, he only notes the second half of the above chart as a fragment of the entire temperature course of the disease.

Where there are distinct symptoms on the part of the mucous membranes these consist of coryza, discharge from the nose, sneezing, swelling of the nasal passages, disturbance of sleep; in small children shortness of breath, and occasionally severe epistaxis. To this is added—which is quite rare in ordinary coryza—a sense of pressure in the eyes, causing rubbing, injection of the conjunctivæ, lachrymation, and photophobia, so that the children ask to have the room darkened. The cough is often quite characteristic of measles; it is dry and paroxysmal and sounds harsh without any signs of

"looseness." Finally, the voice is muffled or is hoarse from the onset, which may always be referred to a superficial catarrh of the larynx. Not always are all of these cardinal symptoms present, often only one or the other, and then only to a very slight extent. A possible disturbance of the general condition is shown in younger children by irritability and crying, in older ones by loss of appetite, lassitude, occasionally by chilliness or chills. Finally, not rarely, vomiting may occur as an initial symptom.

None of these complaints or difficulties has a well developed plastic character, but, rather, at least in the majority of cases, are only feebly developed.

The objective examination, if there be an opportunity to make one, does not show specific lesions in the diseased mucous membranes. The conjunctivæ are often intensely swollen and reddened, mucus and pus are excreted, and stick to the lids, thus causing difficulty in opening the eyes, but a macular character of the redness cannot be noted. If at all present, this is met with in the mucous membrane of the palatine arches and upon the tonsils, but only toward the end of the catarrhal stage shortly before the appearance of the eruption.

All the more valuable, therefore, is a phenomenon which, although not absolutely characteristic of measles (by some authors also noted in rōtheln), is of importance for the eruptive character of the catarrhal process of the mucous membranes. This is the *whitish spots* found upon the inner surface of the cheeks, behind the angle of the mouth. This name may be given to them, as Koplik, who accurately described this symptom, states that they

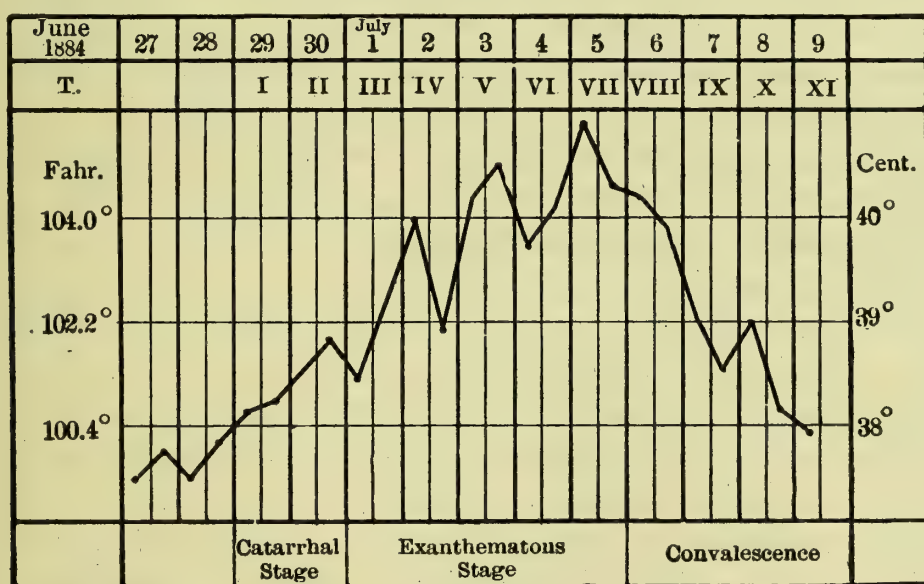


FIG. 19.

appear like fine specks of lime upon the reddened mucous membrane. These spots, found upon reddened areas, are about the size of the head of a pin, raised above the mucous membrane, disseminated, few or many in number, and of a bluish-white or yellowish-white appearance. Sometimes they can only be seen with a good oblique light, but if this area is examined they are often found to be quite prominent. Sometimes they resemble a beginning aphthæ. These spots cannot be wiped away, and if the white deposits are scratched off they are shown to be collections of epithelium which are per-

meated by a turbid mass of detritus. They have previously been described, for example, by Reubold, a pupil of Rhinecker, by Filatow, and others, and they are also mentioned in Gerhardt's text-book, but their diagnostic importance and their regular appearance on the *first* days of measles was first clearly shown by Koplik. They are a very frequent prodromal symptom, and in my clinic were noted in six-sevenths of all cases.

The symptoms of invasion last three days. Toward the end of this first stage, not infrequently before the cutaneous eruption, there appears upon the mucous membrane of the palate an exanthem which consists of individual, deep red serrated spots, separated from one another, inside of which the swollen solitary follicles are noted as individual nodules. This redness which is sometimes confluent and only serrated at the borders occurs particularly in the velum of the palate, but thence distributes itself to some distance over the mucous membrane of the hard palate and but rarely, when quite distinct, affects the tonsils, for example, the surface surrounding the lacuna. This eruption on the palate disappears more rapidly than the cutaneous eruption. It is not of great importance for the diagnosis of measles to recognize this prior to the eruption of the cutaneous exanthem, as it usually only appears with this or at least precedes it only by a very brief period.

Upon the evening of the third day or during the succeeding night the first macules appear upon the skin, most frequently upon the face or about the eyes and mouth, upon the temples and behind the ears. But quite regular cases occur in which the first delicate macules are seen upon the back, whereas the head and face are still free from the eruption. The macules rapidly increase in number and enlarge by coalescence of the smaller and larger spots and now appear upon the entire surface of the body. A distinct sequence of individual parts of the skin may be noted, thus, after the head and neck, the upper trunk and upper arms, then the lower trunk, buttocks, thighs, and, finally, the forearms, lower legs and feet are attacked. The rapidity with which the entire body is covered varies greatly in individual cases, upon the average the maximum of the exanthem is reached in from a day and a half to two days. Upon its first appearance the individual macule of measles is small, scarcely of pin-head size, of a light red color, and round, sometimes, however, even upon its appearance it is of an irregular shape, oval, indented and also serrated. It is not raised above the level of the skin and in children with very white skins it is sharply defined. However, the character of this macule changes rapidly. It becomes darker red, dull brown, and larger, several neighboring macules being combined, and only now does the characteristic appearance of the eruption of measles appear: Lentil-sized, and larger, irregular, serrated, crescent-shaped macules inside of individual ones, in the larger macules mostly three or four conically pointed red millet-seed nodules are seen and felt. The nodules often correspond to hair follicles or to the mouths of sebaceous follicles. These glands secrete more profusely than normal so that the affected cutaneous areas have a slightly greasy feeling. The entire macule is now raised above the surface of the skin (*morbilli elevati*; cases in which this nodular elevation is slight or absent are known as *morbilli laeves*).

Occasionally in place of the nodules, particularly upon the back and chest,

vesicles are formed, then a large number of small spots are found which carry a vesicle in their centre, the exanthem of measles then resembling miliaria.

The whole appearance of the measles patient shows distinct macules at the height of the eruption, the entire skin from head to foot is covered with closely adjoining individual points of the eruption. As the eruption in each part of the body remains at its acme for quite a time the total distribution of measles may be easily observed. No part of the skin remains free, the hairy head and ears as well as the genitalia being covered with the eruption. The back of the hands and the soles of the feet are shown to be most markedly affected.

Upon the trunk and upon the buttocks most frequently—but this phenomenon also occurs upon the face and the extremities—the appearance of the eruption is also altered by the fact that sooner or later the individual serrated macules extend beyond their limit and completely coalesce, forming large groups. This gives these wide cutaneous surfaces an appearance of being uniformly covered by a connected eruption, the consistence differing quite markedly from the spotted skin of ordinary measles. *Confluent measles* is then spoken of. That these have, however, occurred secondarily from the above-mentioned characteristic macules can always be noted upon closer examination, for individual, completely white, usually somewhat serrated cutaneous areas have remained in the midst of this connected mass of redness.

An appearance which is not rare in a quite regular course of the disease consists in the fact that more or less distributed areas of the cutaneous eruption become hemorrhagic. This occurs particularly upon the cheeks, forearms and buttocks, but it may also occur upon any other part of the body. That the vascular change in the macules of measles is combined with a greater permeability of the vessel walls permitting the hemoglobin to pass out (whether this be in the form of the erythrocytes themselves or in the form of dissolved hemoglobin from the corpuscles) may be concluded from the pigmentation of the macules of measles, which for days and even for weeks permit us to still recognize the character of the eruption which has already faded. Not rarely do massive extravasations of blood occur in the area of the eruption. Then the exanthem takes on a dark bluish-red color which gradually turns green or yellow, exactly like any other cutaneous hemorrhage. The change also preserves the exanthem for a long period even into convalescence. This deviation which is without importance for prognosis must not be confounded with the cyanotic appearance of the cutaneous eruption which is always of serious import and which will be described later on.

It is unquestionable that the patient during the acme of the eruption emits a peculiar odor which is variously described by different observers.

With the development of the exanthem the *complete disease* reaches its acme. The temperature at its highest grade reaches 104° F. and often above 104° F., sometimes above 105.5° F., even in ordinary cases, and even during the morning hours of the worst days no remission occurs. In a regular course of the affection the pulse corresponds to the fever without reaching disquieting heights. The general condition and the nervous system are now markedly implicated in the process. The appetite is entirely gone, the patient becomes apathetic toward his surroundings and his own sensations, toward

night somnolence changes to irritability; complaints of headache and pains in the limbs, and not rarely delirium, often of quite severe type, may be noted.

All catarrhal phenomena increase. The mucous membrane of the eyes secretes more markedly, and during the night the eyelids become agglutinated, and can only be opened with great pain and then marked photophobia is present. The nose secretes purulent mucus, which excoriates the nasal openings and the upper lip. Now and then herpes develops about the mouth. The hoarseness is of a high degree; soreness in the larynx or along the larger bronchi is disturbing, but the dry cough which is almost continuous is particularly troublesome to the little patient weakened by fever.

Physical examination shows the existence of a bronchitis of the larger tubes.

The tongue is covered by thick, whitish, viscous masses which during the acme of the disease are often desquamated in serrated flakes so that the smooth red mucous membrane of the tongue is visible beneath. Upon the gums and upon the mucous membrane white deposits appear while the exanthem upon the mucous membrane disappears. Occasionally the eruption upon the skin is accompanied by a paroxysmal diarrhea, as a rule, however, constipation is present.

All the lymph glands of the neck, throat, axilla and inguinal region often enlarge decidedly, the glands may even become painful.

The urine becomes scant, concentrated, shows a sediment and, with a high fever, not rarely contains albumin. Various finer alterations in its composition point to disturbances of metabolism at the height of the disease; thus, the regularly and very markedly developed *diazo-reaction* which occurs in measles, the appearance of copious amounts of *diacetic acid*, of *propeptones*, allow of the conclusion that under the influence of the poison of measles the decomposition of albumin bodies of the organism occurs in a different manner than under normal circumstances.

Of the alterations in the morphology of the blood, mention has already been made; they point to the circulation of foreign toxic substances. That the blood during measles becomes rich in measles antitoxin, Weissbecker believes to have proven by experiments, in having cured severe cases of measles by the inoculation of serum from persons having recovered from that affection. An interrogation point may well be placed after this statement.

The description given above corresponds to the picture of the well developed intense but uncomplicated affection. In individual cases, in general practice, the accompanying phenomena are often much less developed even in instances in which the eruption, as is often the case, is well marked.

In the majority of cases, it is, however, characteristic that the disease develops progressively up to the maximum of the eruption so that the severest period corresponds about to the time at which the exanthem is in full bloom.

From point to point the combat between the organism and the poison of the disease takes place. The areas involved become more numerous, the condition is more and more threatening until a halt is called; and, in fact, this general "halt" takes place rapidly and suddenly in the measles process.

During the same night in which the severest delirium is present, in which the troublesome cough disturbs sleep, the swelling of the eyes and nose gives rise to the greatest discomfort and when the fever is almost unbearable, the entire picture changes suddenly; fever falls, the child sleeps, the cough becomes looser and sweating appears. Upon the next morning the child is without fever, and has a clear mind, appetite begins to reappear and he is ready again to play with his accustomed toys.

Thus the patient with a rapid defervescence of the fever, which in uncomplicated cases often lasts a day and a half instead of half a day, reaches the third period of the affection, the period of convalescence. That this must still be looked upon as belonging to the disease and cannot be designated as a return to health, is founded upon the fact that during the period of defervescence symptoms exist which only slowly disappear and that it is particularly this period in which a great number of complications and sequels originate.

The *catarrhal symptoms* are those which now slowly disappear. The conjunctiva still secretes for a little time, the eyelids still suffer from the influence of the secretion, blepharitis ciliaris occurs, slowly the coryza diminishes, but still a number of days must intervene before the voice becomes clear and cough gradually disappears.

The skin shows a tendency to sweating while the exanthem is disappearing and a pigmentation which has remained fades either rapidly or slowly. The skin is still very sensitive to refrigeration, its effect is regularly shown by an implication of the mucous membranes particularly those of the respiratory system.

Besides this, a peculiar late effect of the poison of measles makes itself felt: namely upon the heart. The frequent pulse, corresponding to the rise in temperature, falls simultaneously with the fever and now becomes abnormally slow and irregular. The exact character of this irregularity has not yet been studied; this arrhythmia disappears after a few days without a permanent injury to the heart remaining behind.

The duration of the period of desquamation cannot be given with absolute certainty. There is no absolute indication by which we may determine the return of complete health and normal resistance. Temperature taking is of no avail here for, as has already been mentioned, the period of convalescence lasts for days and in some cases perhaps for weeks longer than the period of defervescence.

In practice rather than to regard this period as too brief, it will be well to prolong it and to consider it as continuing as long as there are still signs of an acute catarrh of the mucous membranes.

From this, the described picture of the regular course of measles, there are a number of complications and deviations, in those concrete cases, the discussion of which alone gives a correct idea of the actual condition of the process in measles.

DEVIATIONS FROM THE NORMAL COURSE

Even during the *period of incubation*, symptoms may appear, in contrast to the undisturbed health which is usually present. Occasionally this may depend upon accidental conditions, upon catarrhs or other deviations from health which may be due to other causes, such as ordinary colds, influenza, whooping cough, etc. But there are still quite a number of cases in which the infection of measles even during this time makes itself felt by quite a number of disturbances. This may be recognized from the fact that these symptoms arise during the time at which, according to calculations—for example, the opportunity for infection, the later appearance of the eruption—the infection must have taken place.

These are particularly *slight rises in temperature*, which are noted in children in whom regular temperature observations are undertaken because

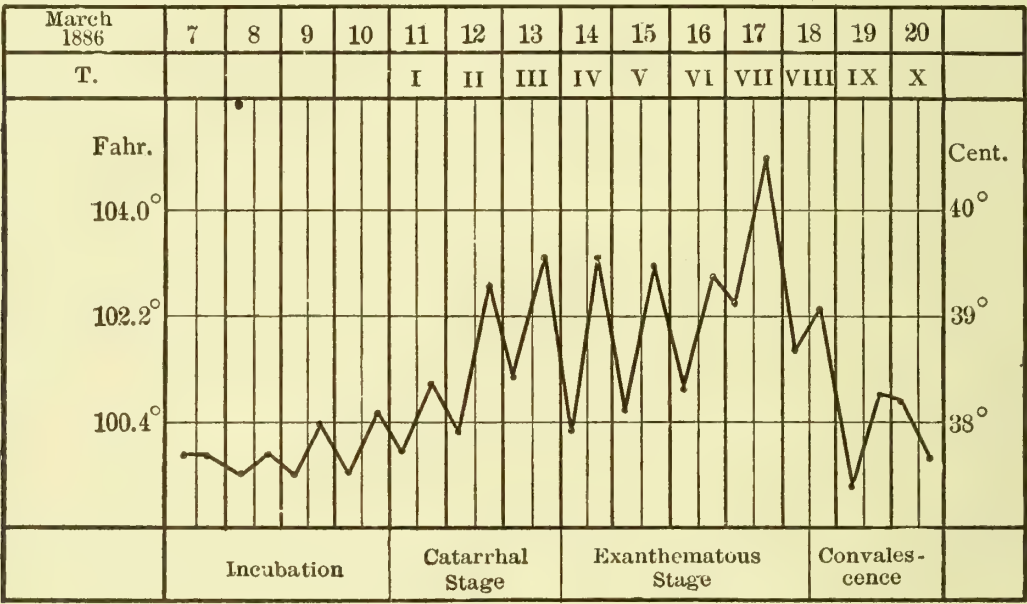


FIG. 20.

it is suspected that they have become infected. Without showing any symptoms of disturbance in health, during some days, or in the evening, occasionally for several succeeding days, temperatures of 100.6° F. to 101.1° F. may be noted in the rectum, with this the daily variations are slight and even in the morning the temperature may reach 100.2° F. to 100.4° F.

In other cases, simultaneously with the slight rises in temperature, the children show other symptoms, particularly disturbances of the same kind as those occurring in the prodromal or catarrhal stages of the disease, but of less intensity, for example, coryza, slight catarrh of the conjunctiva, bloated face, eyes filled with tears or the like. These symptoms disappear and only then, with well developed fever and distinct catarrhal phenomena, does the actual disease begin.

In this manner the disease runs its course, as is shown in the above temperature chart (Fig. 20).

Where there is no opportunity to measure the fever during the period of incubation, we are told that in a case of this kind catarrhal symptoms have

been present for a long time. Very frequently the parents state that cough has been present for a number of days previous to the onset of the disease, which began with pain in the eyes and running of the nose.

It may be readily understood that the catarrhal phenomena and, eventually, also, mild fever are subjectively somewhat more pronounced during the period of incubation, but the chronology of the onset of the disease cannot be determined with certainty from the statements of the patient. Thus, it may be explained that parents say the child has not been well for six, eight or even fourteen days before the appearance of the eruption. Only occasionally does the infection itself appear to be introduced by a febrile period of brief duration which then gives way to an undisturbed period of latency.

An example of this is shown by the following case:

A girl aged seven years, taken ill on October 27th with pains in the throat and lachrymation. Early upon October 24th there was a temperature of 102.2° F., in the evening 103.2° F. Upon October 25th a temperature of 101.1° F.; nothing but a slight redness of the palate could be recognized. Upon October 26th, a temperature of 100.8° F., then complete health; the child returned to school. Upon November 1st, therefore twelve days later, the prodromes of measles appeared and upon November 4th the exanthem of measles was seen.

In an adult aged twenty-five years, ten days before the appearance of the eruption, I once noted severe *arthritic pains*, beginning in the ankles, then occurring in the knees, shoulders, elbows and hands, later attacking the sacral and lumbar regions, and being accompanied with an irregular, not very high fever. With the appearance of a very intense exanthem of measles all pains suddenly disappeared.

The *invasion*, or so-called *prodromal period*, of measles is often characterized by very slight symptoms. Catarrh of the eyes, nose and trachea are then of a minimal nature, as in a very slight coryza, or they may not even be noted at all. There are cases of this kind where the deviation from the normal can only be recognized when regular temperature observations are taken. Where this is not the case the parents very properly assert that the child was quite well prior to the appearance of the eruption. If, thereafter, the entire affection is very mild and also the fever which occurs during the eruption is of brief duration and slight, even the most experienced may come to the wrong conclusion that he is not dealing with measles at all but with *rötheln*.

On the other hand, the disease may begin with unusual, severe disturbances in general health. This occurs particularly in very young children, those up to two years of age, then a rapid, high, continued fever appears, occasionally being ushered in by convulsions, intense catarrh, vomiting, diarrhea and coma. This severe condition lasts for several days of the measles process and is often enough followed by severe complications; but these high febrile prodromes are not necessarily of bad prognosis; sometimes after the appearance of an intense eruption defervescence occurs in the ordinary period of time.

Sometimes the initial disease of the mucous membranes appears with extraordinary severity. The conjunctival catarrh assumes the character of a true blenorrhea, the dry swelling of the mucous membrane becomes so

marked that the children develop a loud sniffing, dyspneic type of respiration (prognostically an unfavorable sign), or the muco-purulent excretion is so profuse that the children lose their rest from the alternate contamination and cleansing of the parts. Occasionally very severe epistaxis occurs, being so marked that tampons are necessary. The transference of the disease of the mucous membranes to the Eustachian tube and to the tympanic cavity may even occur in the prodromal stage. The submucosa of the larynx may be so greatly swollen that serious symptoms of pseudo-croup may usher in the disease; the tracheo-bronchitis may give rise to severe difficulties, particularly causing disturbing cough.

Occasionally foreign symptoms develop. Prodromal eruptions appear, with particular frequency resembling those of miliaria. Occasionally the skin, particularly in cases of children with valvular disease, takes on a peculiar marbled appearance before the beginning of the eruption. Sometimes urticaria-like eruptions appear. In children who suffer from slight dry eczema of the face, the affected areas show a peculiar macular measly appearance one or two days before the true eruption begins.

In place of the catarrh of the upper respiratory mucous membranes or simultaneously developed with this, there is sometimes a simple or purulent inflammation with occasional swelling of the lymphatics at the angle of the lower jaw, then the prodromal fever is higher than ordinary.

Finally the catarrhal stage of measles is now and then abnormally prolonged without other symptoms appearing. Thus it may occur that five, six, even seven days pass before the cutaneous eruption becomes pronounced. Often upon the fourth or fifth day it seems as if the eruption would appear, for around the eyes or nose quite sparse, pale non-characteristic macules appear, but they do not become distinct; the eruption tarries until, finally, two or three days later a distinct and marked exanthem arises, which then usually very rapidly implicates the entire body so that the whole process, nevertheless, is not particularly prolonged. Such an extended prodromal stage always shows fever, this is usually of a remittent type, occasionally, however, it may be of a high continued character. So long as the investigation of such cases shows no objective or subjective signs (for example dyspnea) pointing to an internal complication, there need be no fear on account of the tardiness of the cutaneous eruption. Often this condition is followed by very dense confluent or even a hemorrhagic form of the exanthem.

Deviations from the regular course, having a serious prognostic import, are quite rare during the period of invasion or prodromal stage, and for this reason also a separate examination of this stage of the disease is of value. Such complications occur in both of the following periods, that of the eruption and that of defervescence. In these, however, in the main the nature of the serious changes are not equal. In the period of eruption the great catastrophes occur, the breaking down of the resistance of the entire organism; in the period of defervescence the attacks of individual parts which at the onset show but slight damage of separate organs or parts of organs which, however, by distribution over large areas or invading deeply gain an ominous importance.

Regarding the *period of eruption*, deviations in the form of an especially

mild course are to be noted. In a general, mild affection the cutaneous eruption may be slight and of a fleeting character, whereas, simultaneously, all other phenomena disappear rapidly. There are even infections with measles of a benign character without an eruption; this is shown by the following clinical history.

Hessel, Max, aged three years, taken ill, during the night from January 27th to 28th, with fever, lachrymation, conjunctivitis, headache. Upon the evening of January 30th, temperature 104° F. January 31st, 101.3° F. in the morning, 104.5° F. in the evening. February 1st, 101.5° F. Nothing could be determined; there was marked swelling and redness of the eyes and coryza, evening temperature 102.9° F. February 2d, temperature 101.7° F., early in the morning, continued complaints of the eyes, and headache; marked coryza, cough. Evening temperature 102.6° F. February 3d, 101.5° F., pulse 156. Very restless during the night, much cough, with nausea; evening temperature 103.6° F. February 4th, 100.8° F., condition the same. Posteriorly, over both lower lobes bronchial râles, also some fine râles, evening temperature 101.1° F. February 5th, 100.9° F., in the evening 102.2° F. February 6th, 100.2° F., thence on afebrile course. Complete recovery.

Early upon February 13th, therefore about thirteen days after the onset of the disease, his brother George, aged one year and a half, showed a typical eruption of measles. Max, who had not previously had measles, was not attacked.

In this case, therefore, we were dealing with a febris morbillosa sine morbillis (similar to conditions in other acute exanthemata, such as scarlatina and variola).

The *serious changes* during the *period of eruption* are more important; among these are first to be mentioned those, fortunately rare, cases with a rapidly fatal course. They are analogous to conditions which we meet in scarlatina and other acute infectious diseases and are probably the expression of a most intense intoxication with the virus of measles, or of a lowered resistance of the cells of the body to the poison. Since we have learned, especially by the labors of Ehrlich, Pfeiffer and others, to appreciate the methods by which the organism protects itself in the combat with bacteria and toxins, this explanation can no longer be looked upon as a mere phrase.

In these cases, as, ordinarily, the disease begins with muco-purulent catarrh; in some of my cases high fever was present from the onset, in others the temperature rose gradually. However, from the beginning a marked implication of the sensorium is conspicuous. The children, even during the period of invasion, become decidedly apathetic, sleepy, and lie in bed with their eyes closed, these being often markedly swollen; they have neither appetite nor thirst. Upon the fourth or fifth day of the disease there appear upon the back or other parts of the trunk, some sparse, pale, not very distinct macules, which do not become more developed during the next few days. In spite of this, the fever rises, apathy alternates with nervous unrest; trembling of the extremities, a staring look and strabismus appear; lips and tongue become dry and fuliginous, and now, after a period of from seven to eight days, severe convulsions lasting for hours terminate life, or even without this, death occurs from nervous exhaustion. In the lungs, in some cases, the onset of a bronchitis of the finer tubes may be noted, but this is by no means always the case. Whereas the cutaneous exanthem remains up to death in the undeveloped condition which has been described, in other cases it

only the respiratory function is stimulated and increased. Dilatation of the alæ of the nose, increased respiratory frequency, marked action of the intercostal muscles, besides the movement of the lateral thoracic region, retraction above the region of the insertion of the diaphragm, sometimes general stenotic inspiratory retraction in the jugular and supraclavicular spaces and epigastrium, which almost resemble croup: all this points to a severe implication of the bronchi and the lungs. Examination shows the signs of a gradually extending capillary bronchitis; the heart becomes weaker and weaker, and often with the addition of convulsions, sometimes also of profuse diarrhea, whereas the entire skin becomes flaccid and from the eighth to the tenth day of the disease the fatal issue results. The autopsy then shows the cause of the respiratory affection to be a disseminated inflammation of the mucous membrane of the entire bronchial tree, contrasting markedly with the pallor of the skin. A large number of finest bronchi are plugged with muco-pus and the onset of the inflammatory and atelectatic changes in the lungs can always be determined. The entire process in fact gives a complete impression that the poison of measles, which under normal circumstances produces inflammatory changes in the skin, has taken a false passage and has implanted itself upon the mucous membrane of the bronchial tree. From this first form of the fulminant fatal course, a second one is differentiated in that here a proper resort to treatment may favor the regular localization of the measles poison, whereas in the first instance all therapy is unavailing.

To these general catastrophes I should like to add a third which particularly implicates the lungs, but which in the main is but little recognized, and which, in my opinion, must also be referred to the severity of the measles virus. These cases are rare but I have met with them in several separated measles epidemics. They may be designated as a *rapid necrotic pulmonary inflammation due to measles*. The following clinical history will exemplify the course of this form.

Bode, Emilie, aged one year, both parents healthy; the child having been completely well up to then was attacked, on April 19, 1877, with the usual symptoms of measles, which simultaneously attacked another child living upon the same floor of the house and which in the latter child ran a regular course. With conjunctivitis, which rapidly took on a quite intense character, coryza and cough were present, but no distinct eruption appeared. Moreover, with the fever which was at times high and moderately remittent, on April 25th, over the right, and on April 27th also over the left lower lung, signs of a quite diffuse infiltration appeared which, with continuing fever, caused a marked decline of strength, with frequent collapse, and then attacked the upper lobe. The child became more and more apathetic, complete anorexia occurring, and with closed eyes moaned and complained. Frequent spasmodic grinding of the teeth. Quite severe general condition. Thus the affection lasted several weeks, until May 14th, twenty-six days after the onset of the disease, an eruption of measles appeared, which, however, upon the following day became pale and cyanotic. With increasing asthenia and cardiac dyspnea the child died upon the same day, May 15th.

The necropsy showed the following: The right upper lobe of the lung was adherent to nearly the entire thoracic wall by firm pleuritic adhesions. As was shown by section, it was transformed into masses of cavities containing pus, of the size of a large hazelnut, which proved to be dilated bronchi with very thin walls. The pulmonary tissue lying between, as well as that of the middle lobe, was changed into a mellow whitish-gray to yellow, discolored tissue (but not caseous), in which the original structure could still be discerned, but which showed a decided reduction from the original volume. The left upper lobe was but little altered. Both lower lobes showed the usual condition of

disseminated lobular pneumonia of a yellowish-brown color. In these lobes also a high-graded purulent bronchitis could be noted. The bronchial glands were markedly swollen, medullated, bluish-red; nowhere caseation nor miliary tubercles. Spleen decidedly swollen, pulpy, dark bluish-red. Both kidneys considerably enlarged, with marked yellowish discoloration of the cortical substance; slight intestinal catarrh.

We see, therefore, a child previously healthy, taken ill with prodromal symptoms of measles, and instead of the eruption, a pulmonary affection of a quite peculiar character appears, which in four weeks leads to death; shortly before this a fleeting measly exanthem makes its appearance. Two processes in the severely affected lungs here act together: first, the acute necrosis of the tissue. (In cases occurring later I made a histological examination of the pulmonary tissue and found a non-nucleated appearance of the alveolar exudate as well as of the original dense cellular infiltrated pulmonary tissue.) Secondly, a quite rapid development of bronchiectasis not so much due to an ulceration or suppuration as to a thinning and loss of permeability of the bronchial wall. Taken all together, it is a quite acute and severe lesion which implicates the pulmonary and bronchial tissues to a pronounced extent. It was of great interest to me quite recently (at a meeting of the Society of Naturalists in Hamburg) to see some specimens of pulmonary plague, in which there was the same combination of acute bronchiectasis and necrotic decomposition of the inflamed pulmonary tissue.

In the epidemic of the year 1877 I saw two cases quite analogous to the one described, but with a still more rapid course, they were, however, not so pure as the ones described above, as, besides, caseous bronchial glands were found. In spite of this the acute pulmonary necrosis was not due to tuberculosis. Later I met with similar cases from time to time. I should like to bring these into analogy with the acute inflammatory tissue necrosis of the palate in scarlatina, that refers this development directly to the poison of measles, for the ominous change, as already mentioned, occurs particularly in the beginning and at the height of the disease, at which time mixed infections are not so frequent. Naturally, by this it is not meant to deny that the latter also, under some circumstances, may lead to the severest injury of tissue. I observed a case of necrotic pneumonia, besides malignant endocarditis with cutaneous hemorrhages and renal infarcts, in a nursling aged ten months. The entire process, however, in this case only developed fourteen days after the eruptive period.

This pneumonic form of measles certainly deserves further study; it is sufficient here to call attention to the course, which up till now has been little observed. The prognosis is always ominous to the highest degree.

Before leaving the description of the eruptive period of the disease, *another variation of the exanthem* must be briefly considered. The form which is of little prognostic importance, as well as the important rudimentary forms, the smooth and elevated forms, and the hemorrhagic consistence of the eruption, these have already been described.

The formation of nodules in the individual macule occasionally reaches such an extent that the appearance of the eruption is entirely altered. In each macule that is at all round, a nodule occurs, but of such a size that the face, for example, becomes covered with dense, cloudy, markedly red promi-

nences. The appearance of the patient will then show great similarity to variola. In the case of a young child, upon its buttocks which have become irritated by feces and urine, the nodules in the measles macules spread out, form lentil-sized flat infiltrations, with umbilicated surfaces, and, after the epidermis has become desquamated, are of a shining flat consistency, which may cause confusion with syphilitic eruptions.

Sometimes the exanthem, by a special variety of confluence, shows large macules, the individual spots reaching the size of a ten-cent piece, even the size of a quarter. Sometimes irritation of the entire macule occurs, which then stands out above the other skin like a high plateau, the whole condition very markedly simulating urticaria.

Occasionally in these large individual nodules of measles I have noted pustule formation, which may cause still further errors in diagnosis. The miliaria form of the measles exanthem has already been mentioned.

In some cases, on the other hand, the macules permanently remain as small spots, without confluence, the color then remains light red and the entire appearance of the eruption may bear great similarity to a feebly developed scarlatina.

The relation of measles to pemphigoid cutaneous eruptions is very remarkable, and has been lately emphasized by some authors. I am able to confirm these reports. Not only that not infrequently an eruption of vesicles resembling pemphigus appears in connection with the eruption of measles, but that the eruption of measles itself may appear in the form of a pemphigoid exanthem and run its course.

This is proven by the following case:

On October 23, 1881, George Schilling, aged three years, was attacked by the prodromes of measles, the normal exanthem following, and upon October 26th his brother Herman, aged seven years, was attacked in the same manner.

Simultaneously upon October 26th, their sister Louisa, aged nine months, was attacked with unrest, fever, coryza, hoarseness. Temperature upon October 27th, 100.6° F., in the evening 101.5° F. October 28th, 102.4° F. Upon the face, upon the neck and upon the upper trunk a large number of warty sore spots, partly flaccid vesicles, filled with a thin fluid, being the size of a pea and larger and resembling pemphigus. October 29th, temperature 104.9° F.; the vesicles have not increased, evening temperature 103.2° F. No measles eruption, only upon the buttocks some elevated redness. Evening temperature 105.1° F. October 30th, morning temperature 103.2° F., evening temperature 102.4° F. October 31st, temperature 101.8° F., evening temperature 99.5° F. November 1st, 100.4° F. The vesicles have increased and enlarged, upon the back some the size of a walnut are noted. Upon the buttocks and posterior surface of the legs a raised erythema. Evening temperature 100.6° F. November 2d, 100.6° F., upon the trunk a few new vesicles. Now also upon the lower thighs a few vesicles, evening temperature 99.9° F. November 3d, temperature 99.1° F., a few new vesicles upon the trunk. The old had for the most part ruptured and given rise to erosions. November 4th, no fever, formation of vesicles had ceased, hoarseness still existed.

Of interest, further, is the occurrence of a *relapsing eruption* in measles. I saw this in a girl aged four years, who in the course of a month had two eruptions, and a month and a half later, for the third time, showed an exquisite eruption of measles.

Upon April 16th she was attacked by cough, upon April 27th conjunctivitis with slight fever occurred, and then upon May 1st, with but a single rise in temperature, to 102.7° F., an eruption appeared which distributed itself over the entire body.

Upon May 30th, after all traces of the eruption had disappeared, a second exanthem occurred which was taken to be rubella.

Upon July 15th, the child was taken ill for a third time, with headache and coryza, and, again, upon July 19th, a quite characteristic measly eruption occurred which lasted ten days.

What appears remarkable was that each of the attacks was conspicuously mild regarding fever and accompanying phenomena. Other authors have also described these relapsing forms.

The *desquamation of the skin* after the disappearance of the eruption is very slight and is often entirely concealed by the return of sweating during the stage of convalescence. Fine flaky desquamation of the epidermis may be noted upon the face and neck, upon the buttocks, and not infrequently upon the lower portions of the legs.

Occasionally very marked peeling occurs, particularly in the face, which will then last for days, and may even assume a large lamellar character upon the temples and forehead.

We now reach the deviations in the course and in the *period of convalescence*. This is the true domain of the manifold local disturbances which the entire pathologic process suffers and which, often beginning insignificantly, in their further development reach a life-threatening severity, at other times, naturally, also, beginning abruptly in the course of a few days.

Even where we do not discover the point at once at which the regular process of the reparative changes has been interrupted, there is always a symptom which may be looked upon as a signal of alarm and which under all circumstances should cause a careful investigation: This is an insufficient defervescence or the renewed rise of temperature in the period of convalescence. It cannot be denied that occasionally a certain hesitating drop of the fever by lysis, or also a mild post-febrile course may occur without it being possible to determine a complication, but this is certainly not frequent and, as a rule, the previously mentioned variation of the body temperature may be looked upon as a sign of irregularity in the course of the disease which may cause anxiety for days and weeks.

To present a well-ordered summing up regarding the manifold changes that may occur, it is necessary to present them in a topographico-anatomical review in which it is necessary to remember that often in the individual case quite a number of these secondary conditions may combine.

In the eyes, the catarrh of the conjunctiva is often prolonged. Particularly in somewhat "scrofulous" children the mucous membrane inflammation which leads to the gradual agglutination of the lids may last for weeks and even for months; a stubborn blepharitis ciliaris is added, which, again, is followed by eczema in the surrounding tissues of the eye. Gradually there develop, in case treatment is not effectual, corneal phlyctenula and superficial ulceration, with photophobia, blepharospasm, in fact, the entire symptom-complex of "scrofulous" ophthalmia.

Sometimes, however, the catarrh runs its course as a severe purulent conjunctivitis and marked painful edematous swelling of the lids, a true blenor-rhea of the mucous membrane of the eyes. I once saw the sad case of a boy who in the short period of a two-weeks attack of measles lost the sight of both

eyes by a purulent pan-ophthalmia. The desperate father wanted to sue the physician who treated the child, before it was admitted to the hospital in Leipzig, for he believed—but quite unjustly—that neglect was the cause of the inflammation of the eyes.

More manifold and numerous are the affections of the nasal mucous membranes. An infrequent but unpleasant, and, according to my experience, unfavorable, prognostic course, is shown by the ordinary coryza of measles, when dry swelling of the mucous membrane which may be referred to a more marked inflammation of the submucosa takes place. The children snuffle—it always occurs in earliest childhood—and when drinking or even otherwise when closing the mouth this becomes loud and prominent, the alæ of the nose retract a little with every deep inspiration. Examination shows that there is no secretion in the nose, the opening is covered with dry brown crusts and partly closed.

At other times there is a profuse purulent secretion from the nose, which often predominantly affects the nasal cavity, then this and its surroundings become excoriated, deep ulceration occurs, the adjacent skin often swells to a great extent and shows a hard and glistening upper surface. A smeary or lardaceous exudate is deposited upon the ulcers, ecthyma-like eruptions appear in the vicinity, which again ulcerate or are covered with thick crusts; a process which is accompanied by continued fever, markedly exhausting the affected individual, and while not in itself leading to a fatal outcome, nevertheless causes prolonged invalidism. This condition may be designated as *diphtheroid* of the nasal mucous membranes and its surroundings. Frequently also the surroundings of the mouth take part in this ulcerative process and often complications, profuse diarrhea or pulmonary involvements, are added and may then lead to a lethal outcome.

The distribution of the infectious mucous membrane affection from the nasal cavities to the posterior pharyngeal wall, and, above all, to the Eustachian tube, is still more important. If the inflammatory process has once reached these tissues it rapidly distributes itself to the tympanic cavity and we then have the so very frequent complication of *measles with otitis media* to consider.

This shows itself almost always, by a new rise of the fever, often to a marked height, 104° F., and over, even above 105.8° F., the character, however, being remittent, so that usually in the morning remission occurs, the temperature falling to 102.2° F. or lower, even reaching the normal. The general condition again becomes worse, loss of appetite reappears and to this a certain unrest is added which is especially increased at night. Older children now usually complain of stitches or other pains in the ears, but by no means always, frequently there is a complaint of headache accompanied by hebetude and delirium at night. Small children usually moan continuously, but this is not always pronounced. Not rarely is the peculiar oblique position of the head seen in a unilateral otitis media, especially where, in connection with this, a painful lymph gland swelling develops under the sternocleido mastoid of the same side. The ear speculum rapidly shows the cause of these symptoms. The tympanic membrane has lost its normal lustre, the light reflex has disappeared and, mostly, in the surroundings of the handle

of the malleolus, red or grayish-red swellings are noted. Not rarely may a yellowish or yellowish-brown exudate be seen shining through the tympanic membrane. The pus which usually collects rapidly in the narrow space of the drum after a few days usually ruptures externally through the tympanic membrane. The point of perforation is most frequently situated in the posterior lower quadrant.

Where this spontaneous rupture does not occur, the catarrh of the tympanic cavity with a moderately severe, more mucoid, inflammation may leave spontaneously, the fever disappearing by lysis. If, however, the fever reaches to its former height, then the artificial opening of the tympanic membrane must not be neglected, for, otherwise, further dangers threaten. The infectious inflammation attacks the antrum, insidiously implicates the cells of the mastoid process, and from here easily reaches the transverse sinus or the dura mater or pia mater. I have several times seen a septic sinus thrombosis or subsequent pyemia due to an otitis media, which, a few weeks after the disappearance of the exanthem, terminated the life of the patient.

Or the affection becomes a chronic otorrhea with carious degeneration of the bone, which, by causing suppuration in the brain much later, may result in death. This serious change in the otitis of measles may be prevented by timely interference. Painfulness, slight swelling, or redness of the mastoid process should always receive attention, and, even when these signs are absent, sometimes alone upon the basis of a fever that cannot be otherwise explained, a marked protrusion of the posterior wall of the external auditory meatus, or a very profuse suppuration, we must come to the conclusion to have the mastoid process of the temporal bone opened.

The *oral cavity* may also be implicated in measles. Not very frequently there develops, especially, beside other complications, stomatitis of the mucous membrane of the palate, gums or cheeks. Mistakes may be caused if the mycosis appears in those areas in the period of convalescence of measles, in which in the prodromal stage the characteristic spots have been noted. This eruption is of little importance and is readily removed.

Aphthous stomatitis occasionally gives rise to great difficulties. These painful eruptions may occur in all parts of the mucous membrane of the mouth, they occur particularly upon the gums of the incisor teeth and upon the adjacent inner surface of the lips, as well as upon the anterior part of the tongue, and often result in a very marked edematous swelling of the lips with formation of hemorrhagic fissures, also similar ulcers in their surroundings, as has been described under nasal diphtheroid.

At other times more circumscribed but ulcerative inflammations occur in individual areas of the mouth and from them hemorrhagic infiltrations of the mucous membrane and mucosa are distributed along the gums. The severest form of this secondary mouth affection leads to noma which has a particularly close relation to measles. The description of this condition will follow later on.

Finally, *the larynx* must be considered. That this organ in the first days of the disease may also give rise to symptoms of pseudo-croup has been mentioned; much more frequently, however, in the stage of convalescence there

is a disturbing increase of the laryngeal catarrh. This usually occurs in young children from one to two years of age.

Under continued and, occasionally, very high fever (over 104° F.) the hoarseness which was already present during the stage of eruption changes into complete aphonia so that even crying occurs quite without tone. Beside aphthous oral affections, also ulcerative nasal and lip affections of the variety described above may increase the difficulty. The children always become restless, do not sleep, throw themselves about, and it usually requires a few days until the stenosis of the larynx reaches a certain grade. Respiratory retractions which are not very decided but are still worthy of note occur in the jugular space and in the epigastrium, especially if the child is irritated and as a consequence of this breathes rapidly. Then the inspirations and expirations are accompanied by those sounds which denote a beginning narrowing of the opening of the glottis. Inspection of the oral cavity shows reddening and soon also marked or slight swelling of the palatine and pharyngeal parts, but—in case aphthæ are not present—no deposits or membrane formations can be noted. Now anxious hours and days begin, prior to each visit the physician believes that the time for intubation or tracheotomy will have arrived, and yet no increase of the phenomena of stenosis can be determined. External palpation of the larynx and of the trachea teaches that these parts are very sensitive to touch—therefore, by the superficial plugging of the cartilage, perichondrium and connective tissue they are in a condition of inflammatory infiltration. This clinical picture just described in fact depends upon an inflammation of the mucous membrane of the larynx and the surrounding parts (particularly the *submucosa*), which is not infrequently confirmed by the autopsy. The changes which are found in the cadaver in cases of this kind are, a rigid, thickened epiglottis, prominent false vocal cords and arytenoid cartilage coverings, all showing a deep dark redness and being permeated by hemorrhages and showing a velvet-like swelling of the markedly reddened mucous membrane of the trachea from above downward to the bifurcation. It is, therefore, the severe *inflammatory* swelling of the supra- and subglottic covering of the membrane which causes this form of the disease that, clinically, may well be designated as laryngeal croup. It is also well in the treatment of cases of this kind to adhere to this conception for they are effectually influenced by a proper antiphlogistic therapy (blood letting).

Croup occurring in measles, with *membrane formation* upon the vocal cords and upon the rest of the laryngeal mucous membrane, according to my observation, owes its origin to a *diphtheritic* infection, and for this reason will be considered later on.

In older children the laryngeal affection does not readily assume such a threatening character as in the very young, for, in the first place, the phlegmonous inflammation does not readily lead to stenotic phenomena on account of the greater space of the glottis, and, secondly, the danger of the addition of distributed inflammatory foci in the lungs is a slighter one. Here, occasionally, the very marked tenacity of the hoarseness, which may lead to complete aphonia, and of the laryngeal cough, which may last for weeks and even for months, gives rise to fear. But, finally—at least in the cases that I have

seen—complete restitution occurs. Anatomically the condition is due to a simple chronic catarrh without ulcer formation.

It is now generally assumed, and I favor this view, that all of the enumerated complications and distributions of the catarrh, which were originally due to the toxin of measles, are no longer results of this but are due to the addition of new deleterious effects, and especially to the action of secondary bacterial infections. It does not appear that we are dealing so much with peculiar forms as with those generators of suppuration and inflammation which are found everywhere and particularly in the nasal and oral cavities of both the healthy and the sick: staphylococci, streptococci, pneumococci, coli varieties and the like. The possibility of their successful onslaught is prepared by the attack of measles and perhaps particularly increased by external physical deleterious influences (refrigeration).

The same is true also of the numerous and especially important affections on the part of the *bronchi and lungs*, which appear unexpectedly in the period of convalescence. Often, however, these disturbances have already begun during the acme of the eruption and increase later; nevertheless, it frequently happens that nothing points to the complication which develops later on.

The most dangerous form under which the pulmonary complication appears is the catarrhal inflammation of the smallest bronchi, which rapidly distributes itself over the entire bronchial tree, *acute capillary bronchitis* (bronchiolitis, suffocative catarrh). It attacks particularly weak children in the first and second years of life, but it by no means spares older children. Thus I once saw a boy aged seven years, for over a week after measles had disappeared show a dyspnea with 80 respirations per minute, being in an exceedingly dangerous condition.

The prodromes are usually without alarming phenomena, often being accompanied with but slight symptoms; the eruption has usually become pale but has appeared over the entire body and then shows a confluent character over the trunk—then the general condition of the child changes. He becomes conspicuously pale, while the remains of the exanthem take on a livid color, the child being restless and very dyspneic; the pale semitransparent alæ of the nose move regularly, the diaphragm heaves, drawing the lower portions of the thorax inward, and the auxiliary muscles of respiration enter into action. The fever does not run very high, hovering about 102.2° F., the pulse, however, shows an unproportional high frequency, rising to 160, 180, even 200 per minute. An examination of the lungs at the onset shows but little regarding the severity of these serious symptoms of disease, but from day to day numerous fine râles are heard, first in the lower posterior parts of the lungs, soon rising higher and higher, and then also being heard in the lateral aspect of the thorax. Tracheal râles are heard at a distance, the cough which becomes feebler and feebler is no longer sufficient to bring up the contents of the bronchial tubes. The unrest and anxiety give way to semiunconsciousness, and the patient lies with half-closed eyes, the bulbæ being turned upward; occasionally general convulsions occur, the pulse becomes smaller and smaller, and gradually life ceases after but a few days of this condition. At the autopsy no changes, or but slight ones, are found in the lungs, but the smaller and finest bronchi are filled by a tough muco-

purulent secretion from the inflamed mucous membranes. Two-thirds to three-quarters of the bronchial tree may show this condition; the anterior upper parts are most resistant and remain permeable to air.

The course is less rapid if the inflammatory mucous membrane affection does not disseminate itself rapidly over the greatest portion of the bronchi but limits itself to one or the other pulmonary lobes. Then, primarily, a *circumscribed capillary bronchitis* arises, which, with a somewhat prolonged duration, is always connected with the sequelæ of catarrhal pneumonia in one area, atelectasis in a second, and alveolar dilatation at a third point. At the necropsy a high grade hyperemia of the vessels in the pulmonary area may be determined, from which it is concluded that during life a large part of the amount of blood has accumulated here and has become unsuitable for the function of internal respiration, besides having caused increased labor in the mechanism of the circulation. Finally, the rapidly appearing cellular infiltration of the pulmonary tissue in the surroundings of the diseased bronchi reaches such an extent that the inflammatory irritation has not only affected the surface of the mucous membrane but has permeated into the depths of the same.

The clinical picture is somewhat less fulminant than in the former instance; it is true, fever, increased rapidity of the pulse and dyspnea show the nature and the seat of the affection which has followed measles, but the fever, although it may show exacerbations, is markedly remittent and even intermittent, and the other symptoms are of a more moderate grade. Physical examination usually reveals the principal pulmonary portion affected; profuse loud, coarse, and fine râles are noted usually in the dependent portions of the lower lobes, to which there is rapidly added a diminution of the resonance on percussion, with the appearance of broncho-vesicular breathing or even pure bronchial breathing, which completes the diagnosis of the implication of a more or less large pulmonary division. The general condition is commonly greatly disturbed, lassitude, irritability, anorexia and insomnia being accompaniments of the local condition. A distressing cough helps to diminish the powers of the little patient, and the condition is made worse by inflammations of the mouth, severe laryngitis or by intense intestinal catarrh. However, this form of morbilli pneumonia after a series of several days often enough terminates in recovery.

The favorable outcome is less frequent in those cases in which the severity of the infection rapidly shows a distribution of the inflammation over an entire lobe of the lung or frequently over two or more lobes. This may usually be recognized in a very brief time as the physical signs develop very rapidly in this condition. In such instances, similar to lobar fibrinous pneumonia, there is marked dulness upon one or both sides which may also take in the lateral aspect of the thorax, sometimes also showing lobar catarrhal infiltrations of an upper lobe; with this there is high bronchial respiration in the area of dulness, besides which, however, many râles may be heard at various areas. The fever has a more continued character and is high, but it may also assume another form. The pulse is very frequent, the respiration sighing and it appears to be painful, also upon palpation and in percussion of the affected parts the patients complain of pain. Exhaustion occurs more

rapidly than in the previously described variety; the tongue becomes dry. The lips show sordes; frequently galloping respiration accompanied by sighing; in older children there is prolonged delirium, in younger children convulsions occur. Anorexia is complete, but severe thirst compels the children to consume the fluid nourishment which is given them. The urine is scant and concentrated. In spite of the severity of these phenomena, even this lobar form of post-measles pneumonia is endured longer than the first described capillary bronchitis; strong children may even finally recover from the condition. It is worthy of note that after defervescence the absorption of the exudate in a pulmonary lobe which has been infiltrated in this manner may require weeks and even months before complete recovery finally takes place.

But, unfortunately, as may be only too frequently demonstrated by autopsy, it is seen that in fact the condition is due to a lobar pneumonia, of two or even three lobes, in which, however, the original nature is shown by the lobular appearance of the section, besides the character of the exudation is not infrequently of a mixed nature; fibrinous, hemorrhagico-fibrinous and catarrhal exudations are found side by side and intermingled. The pleura in these cases is always found implicated; thin, fibrino-purulent deposits, and inflammatory cloudiness are found in wide areas; beneath the deposit the pleural tissue is permeated by numerous round hemorrhages from the size of a pin-head to that of a lentil.

Exceptionally large, purulent, or sero-fibrinous, or even hemorrhagic exudates develop.

The digestive organs do not remain free from secondary infection, although this is much rarer. It has already been mentioned that in all intense infections in measles the mucous membrane of the small and large intestines, and especially their lymphatic apparatus, is always implicated. Besides the previously described inflammations of the mouth, the larynx, the bronchi and the lungs, there are invariably found in the cadaver more or less well-developed signs of an implication of the intestinal tract.

Occasionally the digestive tract is attacked alone, whereas the respiratory organs are spared. In some cases, not alone in nurslings but in older children, the entire affection begins, beside with the usual catarrhal phenomena, or even instead of these, with severe vomiting and watery discharges which occur frequently, five or six times daily. In the further course of the affection vomiting ceases but the diarrhea continues during the entire course of the disease and only desists with the disappearance of the exanthem. This diarrhea does not appear to have a particularly unfavorable influence upon the course of the affection. In the case of a child aged two years a severe pneumonia was added, and while from the paralyzed anus the thin yellowish-white contents of the intestinal tract flowed continuously, the child succumbed to the pulmonary inflammation.

More frequently diarrhea occurs during the time of critical defervescence, which may almost be looked upon as a critical discharge. Without markedly influencing the general condition during the time of the disappearance of the exanthem, there are muco-hemorrhagic or muco-purulent stools, being small

in amount but occurring in rapid succession. The condition, however, is of brief duration, a day to a day and a half, and then it disappears, often without treatment. At other times, during the period of convalescence, a few days after the disappearance of the eruption, with the addition of fever, severe abdominal pains, and general illness, a marked diarrhea sets in, with thin, foaming, profuse, at other times sparse, frequent mucus discharges. With suitable diet and treatment this condition is controlled, but usually somewhat prolongs convalescence.

But this is not always the case. Instances occur in which the intestinal affection shows great severity, there is marked tympanitis and painfulness of the abdomen; with this there is high fever, severe implication of the sensorium, a dry tongue, briefly, a condition which markedly resembles the typhoid state. In a case of this kind, in my clinic, I found at the autopsy a severe enteritis with septic processes.

This diarrhea is always unpleasant and of questionable prognosis if it occurs in connection with any severe complication, especially if it implicate the lungs. It requires particular attention, and in young children readily leads to a life-threatening exhaustion provided we do not succeed in rapidly removing the condition.

Finally, the intestinal affection may assume the character of a true dysentery, in a clinical as well as in a pathologico-anatomical respect. It is, however, not unlikely that affections of this kind are not due to the usual but to the specific pathogenic agent. In the year 1892, a child simultaneously suffering from measles and a severe dysentery, was admitted from a children's asylum to the Leipzig Hospital, to the division for measles. In a brief period this affection was transmitted to six other patients, and of the seven children attacked in this manner, five died. The autopsy showed the same changes, a severe hemorrhagic inflammation with a distributed coagulation necrosis of the entire mucous membrane of the large intestine (diphtheria in an anatomical sense), that I saw during the French war in soldiers suffering from dysentery during the sieges of Metz and Paris.

Threatening symptoms rarely occur on the part of the *nervous system*. A moderate grade of implication of the sensorium and of delirium during the mildly febrile exanthematic stage belong to the clinical picture of measles. In nervous children these deliria sometimes occur upon the first day of the initial fever and accompany the period of eruption even if the temperature does not rise very high. In a child aged three years I saw a delirium appear with an evening temperature of 102.7° F.

Severe stupor, a soporous condition, or wild delirium are found more frequently in adults than in children during the acme of the eruption.

Rarely these severe toxic symptoms also occur in children.

In quite a fat girl aged seven years, who had a very intense eruption, I noted two days of complete confusion with severe delirium following the day of the acme of the disease. The girl rose in bed, endeavored to run from the room, cried and fought, had delusions of fear with slight hallucinations which resembled alcoholic delirium, saw a number of maggots moving about upon the ceiling and the like. Gradually she became quieter and, finally, after a brief period she recovered completely.

The delirium occurring during convalescence is more remarkable, this resembling the post-pneumonic disturbances of adults.

In a boy aged six years, at the end of the eruptive stage, in the morning after a fall of temperature (from 104.4° F. to 99.9° F.), there occurred a delirium with hallucinations. He thought that he heard drums and ran to the window to see the soldiers, then from all four corners of the room storks appeared which bit him in the leg; he began to rave and curse, and pulled the hair of his father, who was holding him. This condition lasted the entire day up to five o'clock in the evening. After the use of chloral quiet appeared. During the next days signs of hallucination with mild fever recurred and then the complete normal condition returned.

A more serious symptom is the occurrence of *convulsions* in the course of measles. In the stage of invasion they are rare and, according to Trousseau's experience, are not of unfavorable prognosis. Where, on the other hand, they occur at the time that the eruption should appear, which almost exclusively happens in children from one to two years of age, they are very serious and indicate a very severe general intoxication which almost invariably results in death. I have occasionally seen this in the stage following the eruption, in the second week of the entire affection, as an accompanying symptom of pulmonary or bronchial affection—but not with the same unfavorable prognosis. Often the cases terminated in recovery.

It will always be well to give a guarded prognosis even in these post-morbili convulsions, in view of the experience that measles belongs to those infectious diseases in which encephalitic conditions may arise, for, prior to leading to paralyses, they show themselves first in the form of convulsions.

The skin is not infrequently implicated in the measles process, apart from the described variations of the eruption. Once, in a child aged two years, I saw convalescence retarded by a very intense eruption of miliaria. Occasionally, in children who have been weakened by diarrhea or chronic pneumonic affection, stubborn furunculosis arises, also eruptions resembling pemphigus may appear even a long time after the disappearance of the measles exanthem.

In septic endocarditis, hemorrhagico-necrotic foci of a circumference of several centimetres appear upon the abdominal wall or also upon other parts of the surface of the body.

The severest cutaneous affection, upon the whole very rarely occurring in large number of cases in individual epidemics, is *noma*, *cancrum oris*. Its point of selection is the skin of the cheek and the surroundings of the female genitalia, the large labia and neighboring parts. I once saw it arise from the floor of the mouth beneath the tongue, in a tuberculous child suffering from measles and whooping cough. The point of entrance for the pathogenic agent of this gangrenous condition, which advances with dreadful rapidity, always appears to be an ulcerated area in the mucous membrane, either in that of the cheek near the angle of the mouth, or in the vulva. The poison rapidly passes through the tissues; soon an elastic edema is noted in the affected area of the face opposite the mucous membrane of the cheek, in which first there is a brownish then a blackish area, indicating complete necrosis of the affected portion of the cheek. While this decomposes to a slimy gray green, dreadfully offensive mass, the gangrene advances into the depths of the

tissues and into the surrounding areas, usually in a manner quite painless to the child, but with increasing, finally fatal, exhaustion. For the most part the affection occurs in children that are otherwise cachectic. Regarding the claim lately made connecting the affection with the pathogenic agent of diphtheria, further investigations are necessary.

Occasionally *rheumatic, arthritic* and *cardiac affections* occur in connection with measles, but much more rarely than in the case of scarlatina.

In a somewhat debilitated boy aged eight years, five days after the appearance of the eruption, I saw renewed fever, and two days later both hip joints were attacked with extraordinarily severe pains. Even lifting the bedclothes led to a scene of crying, and an accurate examination of the markedly retracted legs was impossible. We considered it a severe purulent arthritic inflammation. Simultaneously, a soft systolic murmur could be heard in the heart; in the course of four days both anomalies disappeared completely under the use of sodium salicylate.

However, even without inflammation of the joints, in the period of convalescence, benign endocarditis occurs, from which recovery takes place, but under some circumstances it may even lead to permanent valvular disease. Malignant endocarditis is found in individual cases after an especially severe case of necrotic measles pneumonia.

The kidney is but very rarely damaged; at the height of the severe febrile exanthematic stage toxic albuminuria is noted, which, however, rapidly disappears; in the post-eruptive stage the kidney is spared.

In those rare cases in which an infectious nephritis accompanies measles the conditions are the same as in hemorrhagic desquamative scarlatinal nephritis, and, similarly, may remain as a chronic affection.

COMBINATIONS OF MEASLES WITH OTHER SPECIFIC ACUTE OR CHRONIC INFECTIOUS DISEASES

Measles may be combined with other *acute exanthemata*, in that they may either precede or follow the condition, or also that they may run their course *simultaneously* in the same organism. I have seen the latter condition in the case of varicella, vaccinia and scarlatina. In such cases we have the impression that both infections run their course in the same organism without particularly influencing one another. At most, one or the other may show a briefer course than usual. For example:

A boy aged six years was taken ill upon November 20th, with cough and coryza. Remained in bed. Upon November 23d, complained of headache, difficulty in deglutition and hoarseness. Evening temperature upon November 25th, 102° F.; upon November 26th, in the morning 101.5° F., evening 103.4° F.; pains in the eyes. Right tonsil swollen and reddened, pharyngeal catarrh. November 27th, eruption of varicella; morning temperature 101.8° F., evening temperature 103.4° F. November 28th, varicella eruption disappearing. First eruption of measles in the face; temperature 102.9° F., in the evening 104.2° F. November 29th, maximum temperature 103.6° F., evening temperature 103.4° F. November 30th, temperature 103.1° F., evening 100.8° F. December 1st, temperature 99.1° F., eruption of measles disappeared.

Similar conditions may occur in vaccinia.

A girl aged four, who for two years had suffered from infantile cerebral paralysis, upon May 27th was vaccinated while she was in the stage of incubation of measles. June 3d, coryza and cough. June 5th, eruption of measles appeared and developed to its maximum to June 7th; temperature 104.7° F., evening 104.4° F.; June 8th, 102.9° F., evening 100.9° F. The vaccine pustules began to dry. June 9th, 103.4° F., evening 101.1° F., eruption becoming pale. June 10th, 100.8° F., evening 100.2° F. June 11th, 101.8° F., evening 99.9° F. Afebrile thence on. No reason could be found for the "after fever" of measles. It might be referred to vaccinia.

At other times measles disturbs the course of vaccinia, provided the affection occurs soon after vaccination, the measles process itself not remaining uninfluenced, as, for example, in the following case:

Boy aged fifteen months, vaccinated upon July 2d. Upon July 3d, conjunctivitis and cough. The eruption of vaccinia does not develop properly. Only upon July 9th does the eruption of measles show itself, to disappear upon July 14th; during the entire eruptive period, fever (up to 103.5° F.) and marked dyspnea are present.

Upon July 10th, the eruption of vaccinia appears as it would in other cases upon the fourth or fifth day; upon July 12th, the areola appears, the pustules being well developed upon July 14th. On July 15th desiccation occurs. Continued fever which is prolonged to July 24th by a suppurative otitis media.

To diagnosticate the simultaneous course of measles and scarlatina is always very difficult, still I believe I have observed cases of this kind, the double character of which could be discerned by the symptoms and the subsequent sequels. I have certainly observed the appearance of both exanthems at the same time in the same family. A girl aged one year showed a normal attack of measles (catarrhal symptoms being present during the stage of incubation) without being affected by scarlatina before or afterward, whereas two older children suffered from scarlatina.

If the exanthems succeed each other, the course of the affection depends in the main upon whether the severer infection or the milder one follows. In the former case the prognosis is always uncertain. Measles following varicella more readily takes an unfavorable course and shows complications than vice versa. Naturally, if varicella occurs during an irregular attack of measles this is capable of aggravating and of prolonging an existing bronchitis or pneumonia.

Of 10 cases of measles in my clinic, occurring in connection with scarlatina, 1 died. Of 10 cases of scarlatina following measles, 4 died.

Measles may combine with other acute cutaneous eruptions. Twice in the same epidemic I saw a very intense erythema exsudativum multiforme appear in the stage of convalescence of measles; once eight days after, the second time twenty days after the maximum of measles had been reached, in both cases lasting several weeks. Herpes zoster, etc., also occurred.

According to my experience, one of the most serious combinations is that of measles with *diphtheria*. I cannot escape the impression that the organism attacked by measles offers less resistance to the intoxication and infection from diphtheria. The aid which a specific treatment usually furnishes in so excellent a manner in overcoming diphtheria is of less value in the case

of patients suffering from measles and diphtheria. Even passive immunization gives protection but for a very short time. As soon as diphtheria occurs in connection with measles it shows a tendency to wide distribution, to a rapid implication of the larynx, quickly descending into the bronchi.

Wherever I have had an opportunity for a bacteriological examination, all cases of so-called *morbilli-croup*, in which there is an active formation of membranes, have shown, by the presence of diphtheria bacilli, that they were of a diphtheritic nature. In no other case have I seen the propagation of a diphtheria exudate from the tonsils to the bronchi in all its divisions, into all lobes of the lungs, in the course of twenty-four hours, except in a girl aged four years, who upon the day of the maximum in the eruption of measles showed the first coating upon the uvula and upon the next afternoon succumbed, showing a temperature of 107.6° F. Her elder sister who had previously had an attack of measles and at the same time was suffering from a severe attack of diphtheria recovered.

The course of diphtheria in measles is then particularly fulminant and markedly febrile when it occurs at the acme of the period of eruption or just prior to this. If the second infection occurs during a later period in measles it may resemble the course of the usual forms of the disease. Very frequently, in these cases the palate and pharynx remain free from membrane formation, the infection from the onset at once attacking the larynx.

But even then, when measles follows diphtheria with an almost simultaneous infection, both diseases may influence each other in a very ominous manner.

A strong boy aged seven years, in good circumstances, taken ill upon February 18th, from diphtheria, which rapidly assumed large dimensions in the pharynx. On February 20th he received 600 antitoxin units, and on February 21st, after I had visited him for the first time, he at once received 1,500 more. On February 23d he had attacks of fear, without actual symptoms of stenosis, due to marked swelling and formation of membrane in the pharyngeal parts. Moderate albuminuria, then improvement. Upon February 27th, renewed fever. Upon March 2d an eruption of measles appeared, at once severe apathy and high graded asthenia occurred; gallop rhythm. During the night from March 4th to 5th embolism of the left crural artery; absence of pulse up to the inguinal region, severe pain. During the night, from March 8th to 9th, death occurred. In this case the periods of infection with the contagium of measles and diphtheria were close together.

Another very undesirable combination is that of measles and *whooping cough*. As both affections implicate the same mucous membrane areas their influences increase the difficulties and lead to the great danger of severe complications on the part of the lungs and bronchi. It also appears to be the rule here that the combination shows more unfavorable prospects in cases in which the more intense infection—and measles may be properly looked upon as the more severe—is added to the milder, than if whooping cough occurs in connection with measles.

In the former case, particularly in children in the first years of life, an incomplete development of the cutaneous eruption is apt to occur or the eruption is retarded, going hand in hand with a fulminant development of a very extended bronchiolitis which rapidly leads to death. In the second instance another danger is present, the catarrhal inflammation of the bronchi

and lungs, which is due to the measles process, or which has only developed in connection with the appearance of whooping cough, readily takes a sub-acute or chronic character, thus prolonging the total affection for weeks or even for months. Then chronic indurative processes, particularly of the lower lobes, with the formation of cylindrical bronchiectases occur, and then, as well in connection with the local phenomena as with the general condition, with the continued fever and the high graded emaciation, the affection may very closely resemble tuberculous phthisis.

Finally, the connection of *tuberculous infection* with the measles process must be considered. The influence of this acute infection upon tuberculosis is most clearly recognized in those cases in which it attacks the child that suffers from a latent or quiescent tuberculosis of the bronchial glands. Here it awakens to new life—naturally, up to this time in a manner by no means clear—the quiescent germs of the chronic infectious disease. By way of the lymph channels, or from a caseous area of the capsule of the gland, they reach the surrounding areas, and here give rise to a local miliary tuberculosis, which, if the lethal termination occur soon after the onset of measles, brought about by other complications, may be found in the earlier stages or also, upon a rupture into a bronchus, may show recent tuberculous pneumonia.

An example of such connection is furnished by the following case:

Arthur Gr. began to cough at the age of eleven months. Then he had an attack of varicella. In the second half of the twelfth month the cough was aggravated. In January, 1880, a child aged one year, which was very pale and miserable, with a profuse rattling cough, and high irregular fever, but without signs of an implication of the final bronchi was seen. This condition continued for nearly a month, then the cough disappeared, but later frequently returned. Strength and weight, however, increased in a satisfactory manner. At the beginning of June he was attacked by measles. On June 3d the eruption appeared, a disseminated bronchitis was added, and upon June 8th the child was found dead in bed. **AUTOPSY.** Child still well nourished. In the lower lobes both lungs show short and firm pleuritic adhesions. Left upper and right lower lobe show flaccid infiltrations, beneath which there is a large caseous focus about 1 c.c. in diameter. Right middle lobe shows flaccid infiltration, partly atelectatic. A very large gland at the bifurcation of the trachea shows complete caseation, one half of which is softened. Quite recent development of tubercles in the spleen and in the liver. Mesenteric glands swollen but nowhere caseous.

In another series of cases the first symptoms of a "*scrofulous*" mucous membrane inflammation occur directly in connection with measles, for example, stubborn conjunctivitis palpebrarum, then phlyctena and ulceration of the cornea, with severe eczema about the eyes, the face and the head appear. Now the cervical lymphatics enlarge, cold abscesses develop, and a few weeks later suddenly the neck is seen to swell, and a *tumor albus* develops. Again, a few months later an individual attacked in this manner may develop a tuberculous meningitis and succumb. Here the condition appears to be reversed; measles has attacked a previously healthy child, and only on account of the acute infection does the individual become favorably influenced for the entrance of the tubercle bacillus; in the exanthem described, the germ may enter injured areas of the skin or the mucous membrane of the nose or eyes. Much more doubtful, and as yet not determined by accurate observation, is

the direct infection of the lungs and the bronchial glands by tuberculosis during an attack of measles. The fact must be looked upon with certainty, that not rarely children as well as adults that have been entirely well previous to an infection by measles, show the first signs of a beginning pulmonary affection after the disease has run its course. Among the acute infections, particularly measles with whooping cough takes the first place.

Perhaps the following case of previously diseased lungs, as during an attack of measles, may be looked upon as an immediate tubercular infection.

A child aged two years, that from the end of its first year of life frequently suffered from bronchitis, is admitted to the clinic with the symptoms of a fibroid chronic pneumonia of the left lower lobe. After the onset of phenomena of marked dulness, which remain about the same, so that empyema is constantly suspected, an aspiration proves negative; some time later, the symptoms of cavity formation occur in the affected lobe. Dozens of times the expectoration is examined for tubercle bacilli with negative results. The improvement in the general condition and the increase in weight are opposed to the diagnosis of tuberculosis, therefore, a diagnosis of atrophy of the lung with bronchiectasis is made. When three years of age, upon November 28th, the child had an attack of measles. Readmitted to the clinic upon December 12th, fever returned and emaciation was rapid. Now, to our surprise, the examination of the expectoration showed numerous tubercle bacilli. At the autopsy it was shown that a high-graded bronchiectatic condition, with secondary atrophy of the left lung, was present, because in the markedly swollen bronchial glands, as well as in the healthy lung, a moderate amount of fresh young tubercle nodules were found disseminated. In the preparation which was examined by Virchow a caseous focus could not be discovered.

The possibility of a special liability of the eruptive and convalescent stages of measles (perhaps even of the prior stage) to a tuberculous infection gives a very important direction to practical treatment. The little patients, particularly at this time, must be guarded, with special care, against contact with tubercular patients.

DIAGNOSIS

The recognition of measles during the time of the eruption is easy in general for the physician who has seen a number of cases. The art of recognizing cutaneous eruptions rapidly and correctly cannot be taught by books, no detailed description, no matter how skilfully the words are chosen, not even the reproduction by means of pictures, but exclusively and alone can this be taught by clinical experience. This is also true of measles. The configuration of the individual points in the eruption, their influence upon the surrounding areas, the distribution over the body are, however, so characteristic that even in the examination of a few cases the well developed eruption may be recognized by the beginner, even by the layman. Nevertheless, marked diagnostic difficulties even occur to the most experienced; perhaps more rarely in the case of the child than in the adult. Here in some cases the individual macule of measles, particularly in the first appearance on the face, is so markedly infiltrated that a number of distinct but very close nodules upon the forehead, eyelids, cheeks, nose and the surroundings of the mouth, which are intensely red and have a glistening appearance, give such an impression that the experienced observer is more likely to consider a beginning smallpox than an attack of measles. Even to-day there remains in my memory the horror

of a very sensitive, nervous musician who, during the time of an epidemic of smallpox, was admitted late at night to the Leipzig Hospital, and placed in the smallpox division, but whom I was able to free from his unpleasant surroundings on the next morning, fortunately without having acquired smallpox in addition to his measles. At another time I observed in a student who had 15 to 20 large bright nodules distributed over his entire body, exactly like a beginning varioloid, the eruption being surrounded by a red areola, that only upon the succeeding day was the first appearance of a very well developed eruption of measles noted in the surrounding of the nodules.

A second difficulty is occasionally due to the differentiation from scarlatina. Sometimes measles—but quite rarely—may retain its original small macular character without the larger serrated figures appearing, the entire eruption then resembling scarlatina. If then, accidentally, in place of the usual catarrh, the pharynx particularly is intensely red or even a lacunar tonsillitis appears, the differential diagnosis may be exceedingly difficult, a condition which I have seen. Then it is always important that the surroundings of the mouth and chin show the same features as the rest of the eruption, these parts remaining free in scarlatina, whereas in measles they are always implicated.

The entirely confluent measles, in which the trunk, upper arm and thigh show themselves as covered by a continuous intense redness, may also confuse a less experienced observer, but the expert will note that in some few completely normal areas, white points in the skin are present in the midst of these red surfaces, this being the appearance in measles, and that if upon pressure over the red areas the small deep reddened points do not return first, that scarlatina is not present. The differentiation may become very difficult in the case of *rudimentary* exanthems, that occur only upon the arms and legs, conditions that happen in both diseases. The exact determination of the accompanying phenomena, particularly those relating to the mucous membranes, must then clear up the situation.

Rötheln in general is of a much lighter color than measles, although the appearance of the individual macules is often very similar, besides fever is usually absent in rubella.

Great similarity is shown by the individual cases of *serum exanthem*, such as we meet with not infrequently in the specific treatment of diphtheria. The previous affection and the absence of the characteristic catarrh lead to the recognition of the proper affection.

The exanthems occurring in the course of other infectious diseases may resemble measles, for instance in the case of epidemic cerebrospinal meningitis. Quite frequently the “septic” cutaneous eruptions which occur in severe intestinal affections of nurslings show a similarity to measles and may very readily lead to mistakes in diagnosis.

Further, urticaria belongs to the affections which may resemble measles.

Finally, drug eruptions must be considered, for example, those occurring after *antipyrin* and analogous drugs, producing morbilloid eruptions, but care must be exercised not to carry this *finesse* too far. In the instance of a case of whooping cough, in which the child was treated with quinin, a very experienced colleague could not be convinced that an eruption which had

appeared was due to measles. As, however, some time later the brother of the patient was attacked with the same eruption, the physician had to admit his error, but the family lost entire confidence in him.

All the previously mentioned difficulties play an important rôle in the case of the individual physician who makes an error, and such mistakes are invariably remembered. But, in general, they are rare and seldom lead to mistakes in treatment, for the careful physician will always delay making a positive decision and will always, under all circumstances, treat the case as an infectious disease.

It is unfortunate that the diagnosis of measles is so uncertain before the appearance of an eruption and prior to the incubation, as well as during the first day of the disease; for during this time the patient is already a menace to those about him, perhaps to the same extent as at the height of the disease, as most contagions occur particularly during the period of invasion, which circumstance we should like to avoid. The appearance of a catarrh, with pains in the eyes and lachrymation, especially in a season in which measles is epidemic, should always be suspicious. The only characteristic symptoms of the prodromal period are the fine spots upon the mucous membranes of the cheeks (Koplik's symptom). Only frequently does it happen that they are not present upon the first day, or are so feebly developed that they are of no value in diagnosis; but upon the second day of the disease they are usually present. In a suspicious coryza we should not omit, at least where we desire to protect other children, to carefully examine the mucous membrane of the cheek. The delicate eruption can only be seen with great difficulty by gaslight. It is best seen by diffuse daylight or in sunlight.

According to my experience, these spots do not occur in cutaneous eruptions resembling measles, particularly in r  theln; they are, therefore, a valuable diagnostic aid for the diagnosis of the stage of invasion.

PROGNOSIS

Measles represents a comparatively slight, febrile disease, at least regarding the immediate mortality. Hospital experience is capable of showing but insufficient conclusions, as hospitals for contagious diseases as well as children's hospitals in the main admit only severe cases, many of these coming in after the eruptive stage, and particularly because the division for measles in hospitals constantly shows numerous cases of secondary measles, this always unfavorably influencing the mortality. A much clearer picture regarding general prognosis may be gathered from the experiences of district physicians, those practising in a limited population. J  rgenson,¹ in T  bingen, in 868 cases in twenty years, has observed a mortality of 6.1 per cent.; F  rbringer,² in Jena, in one epidemic, only found a mortality of 8.1 per cent. In the district in Leipzig in which I practised for fifteen years, in nearly 600 cases (594) I had a total mortality of 6.5 per cent., therefore, the same mortality as in T  bingen. If it is considered that this character of the disease in the course

¹ Handbuch der speciellen Pathologie und Therapie von *Nothnagel*, Band iv, Thiel 3, Abtheilung 1: Acute Exantheme, 1895.

² *Eulenburg's Real-Encyclop  die*, Artikel Masern.

of two decades has made itself felt in the poor population living under the most unfavorable unhygienic conditions in a large city, it must be admitted that measles is comparatively a benign affection. In hardly any other disease (with the exception of whooping cough) is the course so much affected by the external manner of living of the patient as in measles. In this connection my own statistics are particularly instructive because they may be divided into two periods.

In the first period up till 1884, those portions of the city which composed my district consisted of alleys and cellars and the population was almost exclusively assisted by charity. At that time the mortality was 10.3 per cent. (278 patients). In 1885 the population changed, new streets were broken through, many of the poorest dwellings disappeared and the patients for the most part consisted of better situated workmen and the like. The mortality in the six years of the second period was only 3.1 per cent. (316 patients). In the individual epidemic Jürgenson's mortality varied between 3.7 per cent. and 8.9 per cent.; with me in individual years between 0 per cent. (very small number of cases) and 15 per cent. In private practice among the well-to-do the proportion is decidedly more favorable (according to Fürbringer twice as good).

In the individual case the prognosis depends greatly upon the constitution. Secondary measles are particularly serious; organisms which have suffered on account of malnutrition, bad housing and insufficient care, young children suffering from anemia, severe forms of nephritis, scrofulosa, etc., always have decidedly poorer chances of withstanding the disease.

Regarding the individual phases of the disease no certain prognostic conclusion can be drawn from the stage of invasion. During the period of eruption a poor development or a retarded state of the exanthem is of unfavorable prognosis as well as the appearance of convulsions; the usual severe cerebral symptoms, somnolence, delirium, etc., are not necessarily unfavorable. In the stage of convalescence any continued or returning rise of temperature after the eruption has disappeared denotes an irregularity in the morbid process.

TREATMENT

If the first case of measles has appeared in a family or the first case has arisen in a school, kindergarten or children's asylum, the question that should be primarily asked is whether and how the distribution of the disease may be prevented. The endeavors directed to this point are usually made illusory by the circumstance that the diagnosis of the first cases during the first days of the disease cannot be made and, therefore, the surroundings of the first patients are already exposed to the contagion before we are in a position to adopt prophylactic measures. Thus, in an institution, the disease is not limited to a single case, but a larger or greater number follow and the prophylaxis can only then consist in closing the entire institution. In the family, here and there in an existing epidemic, a probable diagnosis may be made in the first hours and then, eventually, other cases may be prevented from arising.

This may be done if the sick child is brought into a special room, particu-

lar utensils being used for nutrition and nursing and in having special nurses at hand. Then an isolated service for the patient must be carried out strictly, and all communication between well and sick children, particularly also among the surroundings, for at least three weeks must be absolutely restricted. Under such circumstances I have succeeded sometimes in isolating the individual case. If we are dealing with one or more very young or even weak children the attempt ought to be made to isolate the patient. The circumstance is different if a family is threatened, the members of which have advanced beyond the first years of childhood, in such cases I do not regard a strict isolation as necessary, as measles, particularly during the first years of school life, is combined with comparatively slight risks, and as it is very unlikely that an individual child will entirely escape the affection for life. Whereas, in consideration of the same thoughts, the places at which small children collect (day nurseries, kindergartens, asylums, etc.) are to be closed when measles has appeared in these institutions, such a necessity does not exist in the case of schools—except a particularly malignant epidemic is prevalent at the time which would require such a protective measure.

The *treatment* of simple uncomplicated measles may be a purely dietetic one.

It must only be remembered that the disease, on account of a decided implication of large areas of mucous membranes, has a catarrhal character, and that in this respect care is necessary. All possibility of refrigeration, sudden cooling of the skin, wetting without sufficient drying, particularly draughts, are to be avoided. On the other hand, nothing is more important for the favorable course of measles than the entrance of pure fresh air into the sick-room. Both requirements must be carried out by careful nursing, although they appear to collide with each other.

In persons living in poorer circumstances, even in winter it should be insisted upon that a window should remain somewhat open in the sick-room day and night. To prevent a threatening draught a curtain may be hung in front of the window and the bed moved away. According to the means of the patients, these conditions can be carried out better and better until finally two rooms may be had for nursing, the one being used during the day, the other at night, so that the one room may be constantly aired while the patient is in the other room. The patients usually ask for the exclusion of daylight on account of the conjunctival catarrh, this request should be granted but without completely darkening the room, which is still done in some families. By the necessary light which is required from time to time, the eye is only more intensely irritated; and, above all, a necessary airing under such circumstances is impossible.

The temperature of the sick-room may be somewhat higher than in other fevers, about 68° F., but not too high, because the dryness which readily occurs under those circumstances directly damages the larynx and trachea. The skin should rather be kept slightly perspiring by the frequent administration of luke-warm drinks (various forms of tea) than be too dry. The necessary washings are always to be carried out with care, member after member being cleansed and very carefully dried. Bathing had better be avoided in measles—in so far as it is not necessary for curative purposes—on account of the

possibility of refrigeration. Changing the linen must be carefully performed, this being warmed before being placed upon the child. All these precautionary measures are necessary in the period of convalescence as well as in the preceding period, up to the end of the second week. Except in mild cases the patient should not be allowed to leave his bed before two weeks, preferably not before three weeks; and the patient should stay in the room except in warm sunny weather for at least four weeks. This rule is often broken without consulting the physician and without producing harm; but I know of many cases in which the transgression of this measure has avenged itself, often enough seriously. Even after leaving the bed or the room the regained health remains in an unstable equilibrium for a varying time; great care must be taken to prevent the convalescent from coming in contact with tubercular patients or their emanations for at least three months.

The nourishment should be fluid during the fever and consist of milk, which, in children that are averse to taking milk, may have a few drops of coffee or cocoa added. As soon as the fever has disappeared and appetite returns, if there is no contraindication on the part of the intestinal canal, wheat bread and butter, meat soups, fruit soups may be given, later vegetables, cooked meat and zwieback, finally, bread and potatoes.

After leaving the bed and a few days after leaving the room a cleansing bath is given.

The catarrh of the mucous membranes requires treatment. The eyes are to be washed every morning with boiled water, to loosen the adherent lids, and they are then to be moistened with a salve, such as a zinc salve or a simple glycerin salve; simple catarrhal conjunctivitis requires nothing further.

The coryza requires no other treatment than frequent cleansing of the nose with small swabs of cotton, and protecting the lips by a glycerin salve. This salve is to be recommended on account of its permeating into the upper layers of the epidermis and keeping them moist. By ear specialists (Weiss) it has been lately advised to use a small swab of cotton moistened with a $\frac{1}{4}$ per cent. silver nitrate solution and introduced several times daily into the nose, the fluid being expelled by slight pressure so that the fluid slowly flows to the choana and the pharyngeal cavity. This is said to prevent infection of the tubes and otitis media.

The oral cavity is also to be cleansed several times daily, in older children by spraying or gargling, in younger children by gently spraying, a measure which is certainly not without influence in the prevention of secondary bronchial and pulmonary affections. If the skin itches it may be anointed with a lanolin salve with the addition of 1.0 per cent. thymol several times daily.

With this dietetic treatment in uncomplicated measles we may get along without a drop of medicine, at most a stubborn cough which prevents the child from sleeping may render necessary the administration of some syrup of ipecac with about 0.005 to 0.02 sulphate of codein to 50 grams of water, a teaspoonful being given three or four times daily.

However, if complications arise the physician must not content himself with this expectant plan but must adopt energetic measures even though here for the most part the physico-dietetic method is also prominent in the treatment.

In excessively severe catarrh of the eyes, after a careful cleansing of the conjunctival sacs several times daily, the palpebral conjunctiva should be painted with an 0.5 per cent. to 1 per cent. silver nitrate solution (followed by cleansing with boiled water); in the interval, under some circumstances, ice treatment is necessary or the application of corrosive sublimate (1 to 4,000) and if the cornea is threatened, repeated dropping of atropin (0.03 to 10). The eyelids are to be rubbed with Pagenstecher's eye-salve (Hydrargyr. oxydat. flavum 1:10 Ungt. paraffin. or Ungt. leniens).

With an intense marked swelling of the mucous membrane and submucosa, with excoriation and profuse secretion, combined with the coryza, the insufflation of Moritz Schmidt's nose powder is to be recommended (three times daily): Menthol 0.5, sodium sozodol. 1.0 to 2.0, and 20.0 pulvis sacch. Or the careful pouring into the nasal cavity of luke-warm thymol water $\frac{1}{2}$ to 1 per cent. by means of a teaspoon (not to be injected!), or the squeezing from a tampon of cotton which has been moistened with a $\frac{1}{2}$ per cent. solution of silver nitrate. The surroundings of the nose and the upper lip must be protected by the inunction of a covering salve.

Inflammations of the oral cavity, particularly the aphthous forms, besides careful cleansing, require painting with a 2 per cent. to 3 per cent. solution of carbolic acid several times daily. The nurse should be informed that the brush is never to be dipped into the bottle, but a few drops should be poured out into a spoon or bottle or the like and then used.

The first development of noma or cancrum oris is to be treated by an immediate excision of the diseased area, followed by the use of the thermo-cautery. von Ranke has cured three cases in this manner. The condition of the ear requires the greatest attention. It is not necessary after the presence of an otitis media has been discovered by means of the speculum that paracentesis be at once performed. Non-purulent catarrhs of this form recover spontaneously, purulent ones often enough rupture spontaneously. The introduction of a drop of 5 per cent. to 10 per cent. carbolic glycerin solution and the application of a Priessnitz poultice over the anointed ear are frequently sufficient; but it is necessary to watch the condition carefully as, if, with a continued fever upon the first or second day no spontaneous opening of the membrane occurs, paracentesis must be performed. Even afterward the ear must be carefully watched, fresh rises of the temperature, redness, or even pain in the mastoid process, or a possible enlargement of the lymph glands at the anterior or posterior borders of the bone must be looked for so that the diseased portions of the bone and its cavities may be early opened.

The respiratory organs require treatment even more frequently than do the organs of hearing.

In the severe forms of laryngitis in which the submucosa is implicated the methods described below which produce diaphoresis are to be utilized. Local application of heat in the form of poultices, measures which redden the skin, application of mustard plasters, painting with iodine are not to be undervalued. In these cases if we are dealing with somewhat strong individuals or, better, with constitutions that are not too much weakened, I advise local blood-letting. One or two leeches are applied to the region of the larynx

and, according to the condition of strength, the subsequent bleeding is assisted for a longer or shorter time so that 40 to 60 grams of blood are withdrawn. Amelioration always follows this measure and frequently it prevents the development of a serious process. While this measure is being carried out we should never neglect to have the air which is inhaled by the patient in a pure but uniform moist condition (this is best done by repeated spraying at the bedside).

In disease of the bronchi and lungs the various hydrotherapeutic measures are utilized to advantage. In catarrh of the larger bronchi and even in bronchiolitis, Priessnitz compresses changed three to four times daily are very grateful to the patient. According to the height of the fever, they may even be repeated more frequently and then have a cooling action, if the moistened sheet is not covered with india rubber tissue but only the woolen blanket is laid over it.

In severer cases, measures which redden the skin and diaphoretics are to be used. In cases in which the eruption appears tardily or insufficiently or in which it disappears rapidly, whereas increasing dyspnea, etc., denotes disease of the lung, an artificially produced friction of the cutaneous vessels may bring about improvement. According to the condition and strength of the patient, various methods may be adopted. In very weak children the administration of hot drinks, eventually also of a small dose of pilocarpin internally (5 milligrams to 1 centigram), dry enveloping of the whole body, with the exception of the head, in a woolen blanket are of value, these measures being continued so long as sweating in the face occurs; this is followed by careful loosening of the coverings, thorough drying and rest. In stronger children who can stand some heat and in whom a decided irritation of the skin can be endured, the body is first wrapped in a moist sheet, a woolen blanket being placed over this, and the patient thus enveloped then has another covering placed over these so that sweating occurs as soon as possible.

The "derivative" method is more effectual (in a distributed capillary bronchitis, for instance). This consists in the following: About $\frac{1}{2}$ kilogram of fresh ground mustard is placed in 1 litre to $1\frac{1}{2}$ litre of warm water and this is stirred until the oil of mustard develops sufficiently to begin to irritate the eyes and nose. Then a sheet large enough to envelop the entire body is dipped into this mustard water, wrung out and wrapped about the naked body of the child. Or, as in the above case, simple moist linen is used, a woolen blanket being placed over this. This process has the advantage over the mustard bath in that by this method the irritating fumes are not inhaled by the lungs. Where a good reaction has occurred the entire skin of the child up to the neck will be as red as a boiled crab after fifteen to twenty minutes. Now the mustard wrappings are removed and the child is simply enveloped in moist coverings until a good sweating takes place (in from one-half to one hour). The coverings are then removed and the little patient is placed for a short time in a luke-warm bath. If the temperature has risen in the meantime, cold affusions are poured over the chest, head and neck, this being followed by a thorough drying and rest.

This process, at least for the first time, must be superintended by the physician. The last described process is somewhat tedious but shows sur-

prising results; however, it must not be repeated too frequently, at most but once a day, and the child must have complete rest after that for a long time. If after one or two applications the condition of the lungs has not become better nor the eruption more prominent I do not employ the method any further. No good reaction is obtained after the third or fourth attempt and the strength of the child is unnecessarily wasted. However, in cases in which the desired reaction occurs, a repetition upon several succeeding days may be of value.

In place of, or alternating with the derivative diaphoretic procedures, to stimulate inspiration or to bring about deep inspiration which is then followed by strong paroxysms of coughing, cold affusions in the warm bath may be used in the same manner as they are applied in connection with a desired diaphoretic action. According to age, children remain from two to three or five minutes in a warm half bath, of a temperature of 93.5° F., cold affusions (5 to 6 litres in all) being poured over the chest, head and neck. The openings of the ears are to be closed with plugs of cotton. These cold affusions are also of decided use in cases with high fever in which there is marked somnolence, delirium and dry tongue. With a small pulse some alcohol may be given before and after the bath and these baths may be given from four to six times daily.

The action of emetics in bronchitis of the finer tubes is somewhat uncertain. Wine of antimony is best for this purpose, of which a teaspoonful may be given every quarter of an hour until vomiting occurs, but previous to this the child should have a plentiful amount of some warm drink. Local blood-letting in strong children is perhaps more often in place than we are inclined to assume just now. I have had no experience in regard to this. Finally, it is still to be emphasized that in some cases of pulmonary inflammation in measles, with prolonged fever, the so-called antipyretic drugs are of unquestioned value. Here, under some circumstances, they appear to have an antiphlogistic action, in so far as by their administration not only the fever falls but the local phenomena improve and recovery takes place. The following temperature chart (Fig. 22) shows a case of this kind in which antifebrile medication appeared to me to be of decided value.

Thallin was used at that time in the form of injections into the rectum (5 grams of a 5 per cent. solution). Now antipyrin had better be used for the same purpose, 5 centigrams or 2 decigrams daily, according to the age of the patient, or salicylate of sodium 0.1 to 0.5 several times daily, or aspirin in the same dose. It is impossible to say beforehand in which pulmonary complications in measles this medication will be effective. Sometimes it is ineffective, at other times success appears to be marked, but these measures are not to be continued long provided no favorable influence results.

In those cases in measles in which the intestinal phenomena take on a special character, it is valuable, besides the administration of a starchy diet (for example, some of the commercial infant foods), to give for a half or an entire day, every two days, repeated small doses of castor oil (one-half to a teaspoonful) followed by an oily emulsion containing a small quantity of opium. The treatment of nephritis will be described under scarlatina.

Regarding the treatment of sequels and complications, they cannot be

considered in detail here. Only two points are to be emphasized. The great danger to the patient suffering from measles complicated by a diphtheritic affection has already been mentioned, therefore, upon the first suspicion the specific treatment for diphtheria is to be used in large and repeated doses (3,000 antitoxin units several times). Besides it is advisable to at once immunize brothers and sisters of the patient and to repeat this immunization during the duration of the disease and the convalescence (which lasts about six weeks) every fourteen days. The same is true of measles occurring in hospitals where the patients cannot be strictly protected from an infection with diphtheria. The experiences in my clinic have shown that by this methodic immunization, diphtheria which was nearly endemic in the measles pavilion has almost entirely disappeared. It is true we had to shorten the intervals between the immunizing injections to less than three weeks, for

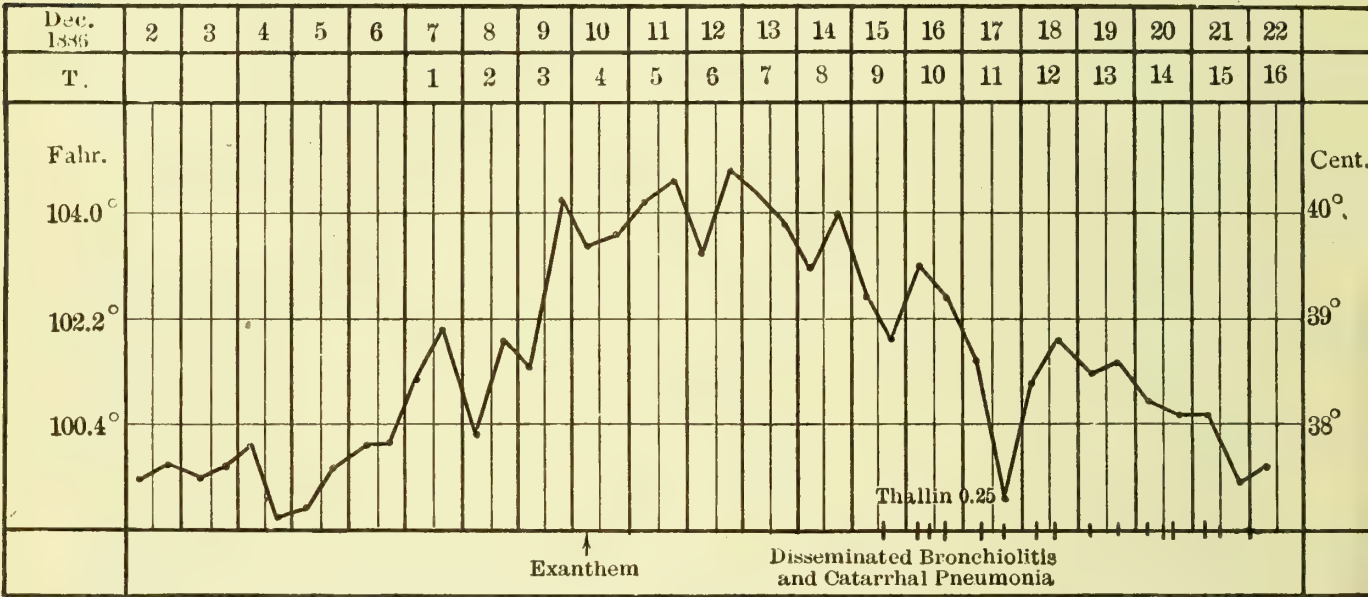


FIG. 22.

a number of times severe infections with diphtheria occurred fourteen to sixteen days after the immunization; it thus appears that the antitoxin in the case of measles in particular is rapidly excreted.

Finally, it is to be emphasized again that in all cases of measles where there is a predisposition to tuberculosis (occurrence of a case of tuberculosis in the family) or where local tuberculosis has already occurred (so-called scrofulosis), the convalescents instead of being isolated for but three or four weeks are to be looked upon as half convalescents for several months and as of very unstable health and their resistance must gradually be increased by good nutrition, residence in fresh pure air and exemption from any laborious activity before they again return to the dangers of ordinary life. To recognize the time when this period has arrived is perhaps possible by an estimation of the body weight, either after the previous weight has been reached and maintained permanently for several weeks or after the child has been brought up to the average weight of its age and maintained at that.

The erection of homes for convalescents in connection with hospitals is an obvious necessity in order to attain this end, especially in case of the poorer classes of the population.

RÖTHELN, RUBELLA, GERMAN MEASLES

By CH. BÄUMLER, FREIBURG

THE conditions of hospitals in which eruptive infectious diseases are treated, as a rule, are such that the student only sees in adults those diseases which, later on in life, he encounters principally among children. This also has its advantages. On the one hand, many peculiarities are noted regarding the appearance and course of eruptive diseases which occur particularly in infancy, such as measles, scarlatina and rubella, which are then of value in judging the condition in children. On the other hand, the study of the previously mentioned diseases in adults is important in a differentio-diagnostic respect, as in them conditions arise in which the decision in the individual case is of far greater importance than in the case of children.

The following history of *rötheln* will serve as a text for the description of the disease:

H. J., locksmith, aged twenty-one, was admitted to the hospital May 18, 1900. He had previously been well, and the day prior to admission, without any other symptoms, with the exception of a mild coryza, noted red spots upon his arms and chest.

Upon admission he had an axillary temperature of 100° F., pulse 100 per minute, and upon the entire face, upon the neck, trunk, and upon the arms, as well as upon the thighs, a light red macular eruption was present. The face showed no diffuse reddening and on the rest of the body the skin was pale between the indented, here and there confluent, spots. At many points in the eruption, the somewhat swollen cutaneous follicles were reddened. The eyelids were swollen, the conjunctiva moderately injected, the upper and lower lips were covered with spots, and the pharyngeal mucous membrane was somewhat reddened; there was no decided swelling.

Bilateral enlargement of the superficial cervical glands.

Nothing abnormal in the organs of the chest, *no catarrhal phenomena.*

Splenic dulness extended 6 cm., border of spleen could be felt.

Urine free from albumin, *no diazo-reaction.*

Temperature, eight o'clock in the evening, 99.7° F.

May 19th: The eruption had almost the same appearance as the day previously. The record states:

Upon the lower legs some few individual spots are noted, the palms and dorsum of the hands are free from eruption, the cervical glands have become somewhat larger, and the inguinal glands appear more or less swollen. The temperature in the morning is 98.6° F., pulse 88, respirations 22.

Evening temperature 98.9° F.

May 20th: Normal temperature and normal pulse (98.4° to 99.2° F., pulse 75), eruption becomes paler and has spread to the lower leg, also upon the dorsum of the foot, in the latter region consisting of small, irregular, partly net-like, arrangement of macules.

May 21st: The clinical history shows that the mucous membrane of the pharynx is still slightly reddened and that the patient complains slightly of pain in deglutition. In the evening a temperature rise to 100.8° F. In the face distinct, small-scaled desquamation.

May 23d: As the remainder of the eruption, only a delicate marbling of the skin is seen, but the pharyngeal mucous membrane is still red, however, without swelling. The cervical lymphatic glands upon the left side are still markedly enlarged, those upon the right to a less extent. Splenic dulness amounts to 5×7 cm. The patient feels perfectly well, has a good appetite, sleeps well and leaves the clinic on May 26th.

This eruptive disease has then shown itself to be an exceedingly mild almost afebrile affection. If the eruption, which was noted by the patient, had not appeared he probably would not have come to the hospital.

Among the *clinical symptoms*, apart from the description of the eruption, I shall especially mention *two* which are of some importance in röteln. These are: First, the *enlargement of the superficial cervical lymphatics* behind the sterno-cleido mastoid; and, second, *the enlargement of the spleen*.

Regarding the lymph glands, in our case the inguinal glands were also found somewhat enlarged. Very probably this glandular enlargement is less common, but those mentioned belong to areas of the body in which enlargement of the lymph glands may be most readily determined. In many cases this may also be noted in the axillary and cubital regions, or even in the small glands under the skin, upon the lateral aspect of the thorax.

This *lymph-gland enlargement* which is never very considerable, but still quite plain, has a certain differentio-diagnostic importance according to the investigations made in this clinic.

In *measles* a lymphatic enlargement does not occur so early, although an enlargement of the lymph-glands occurs after the development of the other symptoms, above all, depending upon the severity of the catarrhal phenomena of the upper air-passages. In *scarlatina* it is not primarily the superficially situated lymph-glands, those situated behind the sterno-cleido mastoid, but those at the angle of the lower jaw and situated in front of the last-named muscle which, in connection with the severe inflammatory condition of the throat, enlarge early and are often even sensitive to pressure.

From this early, usually not considerable, enlargement of the lymph glands, there is to be distinguished a condition that occurs frequently in scarlatina, more rarely in measles, and perhaps also, occasionally, in röteln, a subsequent inflammatory swelling which often terminates in abscess formation. In scarlatina the condition not infrequently shows itself in the third and even in the fourth week after the onset of the disease, after the fever which is in connection with the process has run its course, developing a fresh febrile curve and occasionally arising simultaneously with the phenomena of scarlatinal nephritis.

The lymphatic enlargement in röteln, according to the observations which Clement Dukes made in a school, may be the first symptom of the disease, appearing before the cutaneous eruption.

The *enlargement of the spleen* is but very moderate, but, nevertheless, it is present from the onset of the affection up to the time of convalescence, and, if the contour of the spleen is drawn upon the skin and measured, it cannot be missed. The enlargement is somewhat less than in the case of scarlatina but more marked than in the case of measles in which the enlargement of the spleen, according to our observations, does not go beyond its usual borders. Diagnostically, this may be of importance in doubtful cases as in all acute eruptive diseases the consideration of all the accompanying phenomena, as well as of the eruption, is of the greatest importance. The diagnosis in an acute eruptive disease, especially in childhood, may, under some circum-

stances, be exceedingly difficult and is often combined with great responsibility on the part of the physician.

Compared with measles, and especially with scarlatina, rōtheln is a disease of but very slight importance. According to the very careful investigations of Thomas, Emminghaus, and others, the disease runs its course entirely without fever, in some cases fever with a temperature of 102.2° F. It is highest at the onset of the disease and falls by rapid lysis. Therefore, in the case of rōtheln the fever is not in close connection with the eruption, as is the case in measles, in which the maximum of the acme of the fever is in proportion to the height of the eruption, and, then, if no complications occur to cause a deviation from its usual course, falls by crisis.

In rarer cases of rubella, besides a marked rise in temperature, there may be symptoms which are common to other febrile diseases, being in part dependent upon the individuality of the patient, such as general lassitude, headache and restlessness. Herpes labialis has also been occasionally observed.

Some *sequelæ*, such as eczema, herpes zoster, marked angina tonsillaris, purulent inflammation of the lymph glands, erysipelas, albuminuria, which have here and there been observed, are in no direct connection with the specific rubella infection, which, for the most part, is only the impetus for other infections to appear. These sequelæ, however, are very exceptional. It is the rule that rōtheln is a quite harmless affection, running its course, in many cases, without serious consequences. Therefore, when the diagnosis can be made with certainty from the first appearance of the eruption, although we are dealing with a contagious disease, to which the susceptibility in infancy is a very great one, isolation of the patient is not necessary. On the other hand, in a mild case of scarlet fever, in which we are never quite certain whether serious complications may arise or not, and from which, by transmitting contagion to another, the severest, absolutely fatal form of scarlatina may arise, isolation is imperative. In measles, at least as regards sickly or weak individuals in the cold seasons of the year, in which severe complications are likely, especially on the part of the lungs, isolation is advisable. There are, however, especially in scarlatina, mild forms with but feebly characterized, or but sparse and locally limited eruptions and slight throat phenomena. On account of the mildness of the affection, and perhaps also on account of the variety of the eruption, the danger of diagnosing rōtheln in such a case is especially great if, at the same time, rōtheln is epidemic, but, as is common in large cities, sporadic cases of scarlatina occur from time to time even without an epidemic. Suppose such a case occurs in a child belonging to a family in which there are many children, or occurs in a house in which there are many families with numerous children, or in a large boarding school; rōtheln is diagnosed, the case is looked upon as mild and without serious consequences, isolation is not regarded as necessary, and after the child appears to have recovered he is permitted to return to school. After a few days a brother or a schoolmate is attacked by typical scarlatina and perhaps succumbs rapidly to the severity of the affection or perhaps another child that also came in contact with an apparent rubella patient is affected by mild scarlatina, in the course of which, however, otitis media occurs with a permanent injury to the ear, or an endocarditis develops

which gives rise to chronic valvular disease, or a severe renal inflammation, with uremic phenomena and dropsy appears, from which permanent changes in the kidney remain. Apart from the misfortune to the affected family, what consequences an occurrence of this kind will have for the reputation of the physician need not be enlarged upon. And all this might have been prevented if, by precaution, a positive diagnosis had not been made in the first place, but the patient had been isolated and the further course of the affection observed. What has been said is sufficient to call attention to the responsibility of the physician in cases of this kind.

From this it may be seen that in the diagnosis of eruptive diseases, especially in infancy, it is the duty of the physician to be exceedingly careful to take into consideration all moments and rather err on the side of too much care than, without certain signs of support, to make a positive diagnosis which subsequently proves to be erroneous. Every case that is at all doubtful is to be isolated if there is danger of the presence of a serious disease such as scarlatina or measles or variola, for these must all be taken into consideration in the first stages of the eruption.

Eruption.—The eruption in rötheln must be carefully considered as this is the symptom which impresses the stamp upon the affection, and it is the exanthem which is the most important differentio-diagnostic point in the eruptive diseases in general. Before describing the eruption of rötheln, I must state a fact which should be remembered in every case. It is this, that a cutaneous eruption, perhaps due to a specific cause of an infectious nature, is not alone dependent upon this cause for its appearance, but also upon the structure and condition of the skin of the affected individual, therefore, it is dependent also upon age, general nutritive conditions, circulatory circumstances, the manner of reaction of the nervous system and upon cleanliness. Regarding the skin, it is a well-known fact that in persons of the same age, one may have a fine, and the other a coarse skin; in the former the cutaneous glands are scarcely visible, whereas in the latter they are quite prominent; in one the epidermis is so tender that the capillary net may present itself as a reddish surface, whereas in the other redness is scarcely noted, even in the majority of light complexioned individuals, in parts that are usually prominently red, such as the cheeks, although such individuals may be in the main entirely healthy and by no means anemic.

According to the condition of the skin, the same cause which produces an eruption which primarily causes a macular dilatation of the superficial capillaries of the skin, in which, especially the capillary circle, the mouths of which surround the cutaneous follicles, is more markedly filled with blood will produce quite a varying picture in different persons. I take it for granted that the skin is well cared for and that the appearance and composition of the eruption is not partially concealed by dirt or by disturbances in the circulation and by general asthenic conditions of the organism.

In fact, it must be further noted in regard to the eruptive diseases in question, that the manner and way in which the causative agents act upon the skin are varying and that the variation is influenced by the severity of the affection and, above all, by the virulence of the causative agent of the disease.

Therefore, there may be several circumstances which, in the individual case, may prevent an eruption from appearing in a typical manner, so that it will be well nigh impossible to formulate a diagnosis, except by means of the other conditions: proof of contagion from a well characterized case, the existence of an epidemic, symptoms and prodromal phenomena of a distinct and characteristic kind.

It must be mentioned, above all, that there is no typical uniform eruption in r  theln. Of the three acute eruptive diseases that have been mentioned, the eruption in r  theln varies the most.

Whereas in the case of *measles* there are indented macules, often with a small papular formation due to the follicles of the skin, which stand out prominently with a more or less well defined bluish color, the intensity depending principally upon the severity and distribution of the accompanying catarrh of the respiratory organs, the cyanosis being due to this, the scarlatinal eruption consists of very minute closely intermingled pin-point marks which are found upon the uniformly injected, reddish, discolored skin.

The diffuse reddening is due to a very uniform dilatation of the entire cutaneous capillary net, which, however, is by no means due to a paralysis of the vasomotors. On the contrary, the smallest cutaneous arteries even show an abnormally increased irritability in a similar, but more marked, manner than that which occurs in every febrile reddening of the skin in the most varied febrile diseases, and, next to scarlatina, is most notable in the case of enteric fever. If we run the finger nail or the end of the percussion hammer very gently over the skin there appears very rapidly in a few seconds after the disappearance of the pallor due to the pressure, a broad line 1 to 2 millimetres greater in extent than that produced by the nail or other instrument upon the irritated area; thus designs and words may be drawn upon the skin, these only disappearing in from two to three minutes by a slow redilatation of the previously narrowed vessels.

This sort of an erythema of the skin, naturally, can only occur in r  theln when the disease runs its course with fever as this is a condition which is seen pre-eminently in febrile vascular dilatation. In measles this occurs particularly in the stage of the initial fever, before the appearance of the characteristic eruption. In this diffuse vascular dilatation, the underlying cause is apparently a peculiar action of the pathogenic agent of the disease or the effect of certain toxins produced by it upon the vasomotor apparatus.

The r  theln eruption consists of, at times larger, at other times, smaller, slightly elevated papulo-macules, similar to those of measles but lighter in color, not bluish but of a rose-red color. In some cases these may be very small so that the eruption at first sight resembles scarlatina more than it does measles. Such fine punctiform areas as occur in scarlatina we never see in r  theln. But during the fading of the eruption a phenomenon may appear which is seen in scarlatina and not infrequently in measles, namely very minute punctiform hemorrhages which are situated close together; these are particularly noted in the delicate skin of the axillary region below the external half of the clavicles. They are of no importance in so far as no other severe symptoms are present which point to a hemorrhagic diathesis or to sepsis. The individual macules of which the r  theln eruption consists, for the most part have an irregular serrated limitation in some cases, and in some areas

of the body are so far apart that the entire quite normal appearance of the skin which lies between them may be determined with certainty. The macules give the impression of being slightly raised, but they are not as coarse, as a rule, as those which occur in measles:

Upon the covered parts of the body and at those places at which sweating is apt to occur, sudamina appear, similar to the case in other eruptive diseases.

The distribution of the eruption occurs from the head and face downward. It may, however, especially in cases in which the eruption is but slight, appear first upon the chest and arms, very frequently, even profusely, upon the face, neck, trunk and arms; the eruption is less copious below the knee, and in the lower leg and on the feet but few individual macula can be determined.

Regarding the appearance of the eruption, great variations may occur. One point, however, requires exact observation because it is of great diagnostic importance: In röteln, as also in measles, the region about the mouth (upper and lower lips, point of the nose) is often profusely covered by the eruption, whereas in scarlatina this region of the face is quite conspicuously free from eruption and often remains free from any erythema so that it is conspicuous by its pallor in contrast to the redness of the rest of the face.

Another point, which in a diagnostic respect deserves observation and which I intend to emphasize again, is this, that in the great majority of cases the eruption in rubella is the very first symptom of the disease, whereas in the case of measles the eruption appears only upon the fourth day, and in scarlatina upon the second day after symptoms have appeared. In the case of measles these prodromal symptoms are: fever with coryza and lachrymation, and, according to the height of fever, more or less well developed general malaise, which upon the second and third day, with a decline in the fever, may increase. In scarlatina: very frequently at the onset of the affection, vomiting, fever and pain upon deglutition, with the signs of an "angina faucium"; with very intense reddening and a quite unusual increase in the pulse rate, even out of proportion to the high temperature.

Desquamation in a profuse röteln eruption occurs in the form of small flakes, especially upon the face, neck and chest; it is, however, commonly overlooked if special attention is not paid to it.

If fever is present, the urine may transitorily show traces of albumin. Several times in our hospital, in cases of röteln, we have found the diazo-reaction.

Convalescence in this very mild affection is exceedingly rapid. Remarkable is the reappearance of the eruption after the complete disappearance of the first attack. But these very rare relapses of the disease, as Emminghaus has observed, even with a very rapid course, have their analogy in the relapses of other infectious diseases. Accurate descriptions will be found in the exhaustive autograph on röteln by Johannes Seitz¹ in Zürich.

That in the case of röteln we are dealing with a substantive, specific affection, sharply defined from measles and scarlatina, is now generally accepted. The reasons for the separation of both previously mentioned dis-

¹ Correspondenzblatt für Schweizer Aerzte, Jahrg. xx, 1890.

eases, besides those already enumerated in the description of the symptoms, are these:

1. That r  theln, measles and scarlatina may follow or precede one another in the same individual, that, therefore, neither is a protection from r  theln, nor the latter a protection from either of the other affections, whereas a second attack may occur in measles, as also in scarlatina, but is, however, quite rare;

2. That the period of incubation is a different one from that in the case of the two other affections, in case of r  theln it is about three weeks, seventeen to twenty-one days, in measles only about nine days, and in scarlatina, under some circumstances, only one day, but may also be much longer. The contagious principle of scarlet fever is extraordinarily resistant so that by adhering to clothes and all possible substances (fomites) the transmission is often an indirect one. Between the adherence of the contagious principle to clothes, etc., and its entrance into the body which is still dependent upon all possible eventualities, a varying period of time elapses.

The great variations which the eruption of r  theln shows in different cases, so that it resembles measles, at another time scarlatina, are conditions which increase the difficulties of diagnosis provided the other symptoms and other circumstances are not sufficient to form an opinion. But a new diagnostic difficulty must yet be mentioned.

The Fourth Disease.—A few years ago, while physician to the great boys' school at Rugby in England, thus having an unusually large field of observation for these diseases, Clement Dukes observed that in children that have gone through an attack of r  theln an eruptive disease may appear in which the eruption more closely resembles scarlatina, the other symptoms, however, being against the assumption of scarlatina. If we are dealing with relapses from r  theln it is conspicuous that in the second attack the eruption is quite different from that of the first attack. Dukes suggests that there is possibly still a fourth disease which has something in common with scarlatina and with r  theln, but which is neither one nor the other affection. Other physicians also, principally American and English observers, have, in the course of the last three years, published observations which are calculated to confirm the assumption of a fourth disease ("fourth disease" as Clement Dukes¹ has named the affection). According to Weaver,² the symptoms are, an eruption resembling scarlatina but which also occurs around the mouth, very slight fever, no increase in the pulse rate, no vomiting, no, or but very slight, throat phenomena, no desquamation as in the case of scarlatina, and an absence of the lymphatic gland enlargement of r  theln. F. T. Simpson³ noted the affection several times after scarlatina, in numbers of instances after measles. He observed in several patients of this kind lamellar desquamation.

In children, with their much more susceptible skin and irritable nervous system as compared with adults, there occur, under the influence of the most varied causes, more or less well developed eruptions which, at least in their

¹ Lancet, July 14, 1900.

² Dublin Journal of Med. Science, 1901, VI. Ref. Fortschritte der Med., 1901, Nr. 35.

³ Archives of Pediatrics, Sept., 1901. Ref. in Am. Journ. of Med. Sci., Jan., 1902.

primary stages, may cause confusion with one or the other of the specific eruptive diseases. Especially in small children, during the period of dentition and in seasons in which intestinal catarrh is frequent, with or without febrile phenomena, acute eruptions of brief duration occur, which have been called "*roseola æstiva*" and which may resemble rötheln. In such cases rötheln can only be diagnosticated if, at the same time a rötheln epidemic is present, contagion can be proven, or if from a patient of this sort contagion is spread and an affection resembling rubella appears. In such cases lymphatic enlargement and enlargement of the spleen must be present. Many affections of this kind belong to urticaria or also to erythema multiforme, which latter affection may also run its course with lymphatic enlargement and enlargement of the spleen.

Etiologically, intoxication or autointoxication plays a prominent rôle in these cutaneous eruptions; in erythema multiforme, probably an infection is the cause. It is sufficient to mention the urticaria produced by the eating of strawberries, by the ingestion of certain kinds of sea-food, that form produced by intestinal worms and by digestive disturbances of various kinds, which, in some persons, especially in early youth, is likely to produce this form of eruption. As great as is the difference between a macule of rötheln and of even a small patch of urticaria, it must not be forgotten that, especially in children, any eruption, by friction of the clothes or of the bed and above all, by scratching, the irritated areas may develop papules, even wheals. It must be further remembered that a purely local irritation of the skin, in individuals that are especially susceptible, may cause a distribution over larger areas of the skin, by means of scratching; these primarily local irritations being caused by the bites of insects, by the hairs of certain caterpillars, by ethereal, oleaginous and other vegetable products (thuja—and pinus varieties, primulacea).

Many drugs may, in some individuals, children as well as adults, give rise to eruptions which may distribute themselves over the entire body. On account of its great similarity to measles, the first to be mentioned is the eruption caused by antipyrin, which, in children that have had antipyrin administered to them on account of whooping cough, is not so infrequently observed. In comparison to the eruption of rötheln, the latter is of a darker color and of a more papular character.

The eruption appearing after the injection of diphtheria antitoxin serum may consist of flat macules or papules, and, if at the same time an epidemic of rötheln is present, may give rise to confusion. This eruption, as a rule, shows larger macules than occur in rötheln, usually irregularly distributed over the body and, therefore, more closely resembles erythema multiforme.

In some persons there is a remarkable idiosyncrasy to quinin, in others to mercury, upon internal and external administration. In such persons even minimum doses are sufficient to cause a dermatitis which distributes itself over the entire body, in which only at the onset the erythema is small, macular, soon becoming uniform so that the eruption of scarlatina is closely simulated. This diffuse dermatitis, running its course with fever, is accompanied by a desquamation of the entire epidermis, large flakes coming away, and occasionally, also, by a falling out of the hair and the nails.

In adults, occasionally, the internal administration of cubebs or balsam

copaiba is the cause of a small papular eruption which may resemble measles or urticaria.

In some regions in which typhus fever is endemic, or where it is brought in, measles may be thought of on account of a very profuse eruption, a diffusely livid discoloration of the skin and the papular consistence of individual florescences. These papules, however, are only a small constituent of the eruption, which, in the main, consists of entirely flat, irregularly constituted, livid areas, frequently intermingled with petechia—hence the name petechial typhus. The entire course of the disease, in which the eruption appears only upon the fourth day, the high fever, the marked enlargement of the spleen, the occurrence of typhus fever in the affected region, and the probability that contagion has taken place, enable us, with some slight care, even when measles and r  theln are simultaneously epidemic, to avoid an error, which, on account of the greater transmissibility of typhus fever, might give rise to serious consequences.

In epidemic cerebrospinal meningitis, in some few cases eruptions occur which show a certain similarity to measles or r  theln, as a rule, however, they are more localized to the extremities, a part of the trunk, and more closely resemble erythema multiforme than the previously mentioned eruptive diseases. The presence of an epidemic and of undoubted cerebrospinal inflammatory phenomena is determining above all in the differential diagnosis.

In an adult, during the prevalence of an epidemic of r  theln, a very profuse eruption of roseola syphilitica may appear during the eruptive period of this disease, possibly at the same time with the febrile phenomena, so that the true nature of the disease is concealed and r  theln is thought of. In both, enlargement of the lymphatics and of the spleen is present, in both there may be a somewhat more decided erythematous condition of the palate with slight swelling. But in an eruption appearing so acutely, especially with fever, there is a much more decided general malaise, and, above all, as a rule, severe headache which increases toward night, and the greater gravity of the disease is already noted in the facial expression. Even to the inexperienced, the continuance of the eruption beyond three to four days, its increase, not from above downward but a closer approximation, and an increased development of macules into papules will soon show the true nature of the affection. The examination of all palpable lymph-gland areas will then show at some place in the body a few that are more markedly enlarged, being painless round glands ("indolent buboes"), and, in the peripheral area of the same, the primary lesion may be discovered.

Finally, in septic affections, eruptions which develop rapidly, being of a macular or papular character, not infrequently resembling urticaria, occasionally being hemorrhagic or pustulous, have, at certain stages, some similarity to r  theln or even measles. By an observation of the accompanying phenomena errors may easily be avoided.

It will, therefore, be seen that in the individual case many possibilities must be thought of before an opinion is given in an acute eruptive disease. Above all, every eruption should be accurately examined, and whenever possible by daylight, and the most recent efflorescences should be sought in order to determine its original form, and the further development of the eruption

should be compared with these. The opinion should never be made to depend upon the appearance of the eruption alone, and especially not in those cases in which the affection appears to deviate from the ordinary type of the disease. Above all, the prodromal phenomena of the disease should be inquired into, those that were present before the appearance of the eruption. A complete absence of these, as has already been noted, occurs especially in rötheln, whereas in measles a prodromal stage lasting three days, and in scarlatina, one to two days, is present, accompanied with fever, in measles with catarrh, primarily of the upper respiratory passages, in scarlatina with angina faucium, vomiting and an unusual increase in the pulse rate. But very rarely is there a constitutional disturbance or sore throat, or coryza in rötheln. In measles, before the appearance of the eruption, an alteration of the mucous membrane of the cheeks occurs, which is not observed in the case of scarlatina and rötheln and for this reason is of great diagnostic importance. These are the so-called Koplik's spots: isolated red points the size of the head of a pin with a bluish white or whitish-yellow point in the centre. In every case in which measles is suspected these should be searched for. After the appearance of the eruption they become indistinct or disappear completely, probably under the influence of a more marked hyperemia of the mucous membrane.

Then the other organs (lungs, heart), above all, the spleen and lymph-glands are to be examined; in an examination of the urine the diazo-reaction should not be forgotten.

A careful investigation of the accompanying circumstances, the possibility of contagion within the period which corresponds to the incubation period of the disease should never be neglected, especially in cases in which there has been no previous appearance of the disease in the family to clear the situation.

In every doubtful case a positive diagnosis should not be made, but care should be taken that the disease is not transmitted to others, the patient should be isolated and the diagnostic decision should be deferred for the next few days, until the disease has developed fully. As regards *the treatment* of the patient, nothing will be neglected by this. In those cases in which special symptoms are prominent they must be treated on general principles. High fever and cerebral symptoms in scarlatina and measles may require cold baths, in rötheln symptoms which require treatment almost never occur. In a case of rötheln, therefore, general dietetic hygienic rules are to be followed which are self-evident in any mild affection.

A table is appended which shows the characteristic differences of the three diseases at a glance:

	RÖTHELN	MEASLES	SCARLATINA
I. INCUBATION PERIOD.	17-21 days.	9-11 days.	1-7 days and longer.
II. PRODROMAL SYMPTOMS BEFORE THE APPEARANCE OF THE ERUPTION.	None.	Fever, catarrh of the upper respiratory passages and the conjunctiva.	Vomiting, sore throat, fever, increased rapidity of the pulse.
III. ERUPTION: First appearance.	First day.	Fourth day.	Second day.
Distribution.	First in the face. Upper and lower lips also covered with the eruption.	The same.	First upon the neck and upper parts of the chest, the face, the <i>region about the mouth remaining free.</i>
Character of the eruption.	Macular or punctiform, color light red.	Macular, slightly raised, prominence of the cutaneous follicles, color bluish red.	Finest punctiform areas, close together upon a uniformly reddened skin. Color deep red.
Desquamation.	Ill - defined, small flakes.	Small flakes.	Upon the neck and trunk small flakes, upon the hands and feet, often only after weeks, in the form of large scales (lamellous).
IV. ACCOMPANYING SYMPTOMS: Throat.	Catarrhal reddening.	At the onset, macular reddening then uniform (upon the mucous membrane of the throat, Koplik's spots).	Uniform marked inflammation with more or less swelling, occasionally follicular plugs or membranous deposits. Complicated by diphtheria.
Respiratory organs.	Sometimes catarrh.	Marked catarrh, laryngitis, bronchitis and bronchiolitis. Great tendency to broncho-pneumonia.	
Spleen.	Some enlargement.	No enlargement.	Enlargement.
Lymphatics.	Superficial cervical, auricular, often also other glands, soft and frequently sensitive to the touch.	Not so constantly enlarged as in röteln.	Glands, especially at the angle of the lower jaw enlarged; cervical glands later on, as a complication often with abscess formation.

	RÖTHELN	MEASLES	SCARLATINA
V. FEVER.	Often no fever, or but slight rises in temperature, rarely to 102° F. Highest temperature usually upon the first day.	Prodromal fever lasting three days. Temperature rises with appearance of eruption, maximum of both at the same time.	Highest temperature at the onset.
Defervescence.	Lysis.	Crisis.	Lysis.
VI. COMPLICATIONS AND SEQUELS.	No constant nor frequent ones.	Broncho - pneumonia, otitis media. Tuberculosis of bronchial glands and lungs. General military tuberculosis. Noma. Diphtheria. Rarely nephritis.	Endocarditis. Acute rheumatism. Nephritis. Otitis media. Septicopyemia.

SCARLET FEVER, SCARLATINA

By O. HEUBNER, BERLIN

ETIOLOGY

SCARLATINA is an acute, infectious, contagious, febrile disease, characterized by a scarlet-red cutaneous eruption and by inflammation of the pharyngeal organs. The synonyms of the disease in all civilized languages call particular attention to the peculiarity of the eruption.

But little that is certain is known regarding the history of scarlatina. If we reflect how conspicuously the cutaneous coverings of the body are altered by this affection, it does not appear possible that mention of this disease should have been overlooked in the writings of the Arabians and of the ancient physicians. Descriptions from which the disease may be recognized are only found in medical literature in the second quarter of the seventeenth century (by the German physicians, Sennert and Döring). Sydenham in the last quarter of the same century clearly recognized the peculiarities of the disease.

Observations of the disease showed from the onset a very peculiar changeable character in succeeding epidemics, a diversity which hardly occurs in any other affection. Sydenham, in 1664, did not attribute greater importance to the disease than we show nowadays for rubella (rötheln), and fifteen years later, in the sphere of activity of this great observer, in London, the affection appeared with a severity which was only equalled by the bubonic plague. And if one hundred and fifty years later Bretonneau, a physician of like importance, declared that a scarlet fever patient only died when treated incorrectly, a few years later, when in the presence of an epidemic in which a frightful mortality took place, he was compelled to acknowledge how greatly he had been mistaken. An instructive picture of this periodic, very varying course of the affection, occurring in the same population, is presented by a diagrammatic table of the mortality from scarlatina in Hamburg, compiled by Reincke.¹

The great calamity from which Hamburg suffered in the years 1821, 1831, 1852 and again in 1878 and 1879 from scarlatina is readily recognized, and between these periods there are again very decided diminutions in the danger from scarlatina. The punctuated line added from 1872 on, signifies (in $\frac{1}{10}$ the scale) the morbidity curve (in so far as it could be determined from the report of physicians). It will be noted that the severity of the individual epidemics and the morbidity are by no means parallel. Wherever exact statistical reports have been attained, for example, in Norway, accord-

¹ Die Gesundheitsverhältnisse Hamburgs im neunzehnten Jahrhundert. Hamburg, Sept., 1901, p. 169.

ing to the investigations of Johannessen, which cover a period of sixteen years, it is noted that the affection everywhere shows this very remarkable character of rise and fall of the grade of malignancy. In these observations the morbidity and mortality run quite parallel. It is difficult to recognize this property as a consequence of a varying virulence of the pathogenic agent, it is more probable that other auxiliary causes periodically decidedly increase the susceptibility of the population.

Scarlatina owes its origin to a poison that proliferates anew solely in the human being attacked by scarlatina, whereas outside of the human organism it is capable of maintaining itself in a condition in which it may increase (as a pathogenic organism) but is scarcely ever able to actually proliferate. Previous views, according to which the scarlatinal poison is said to develop in

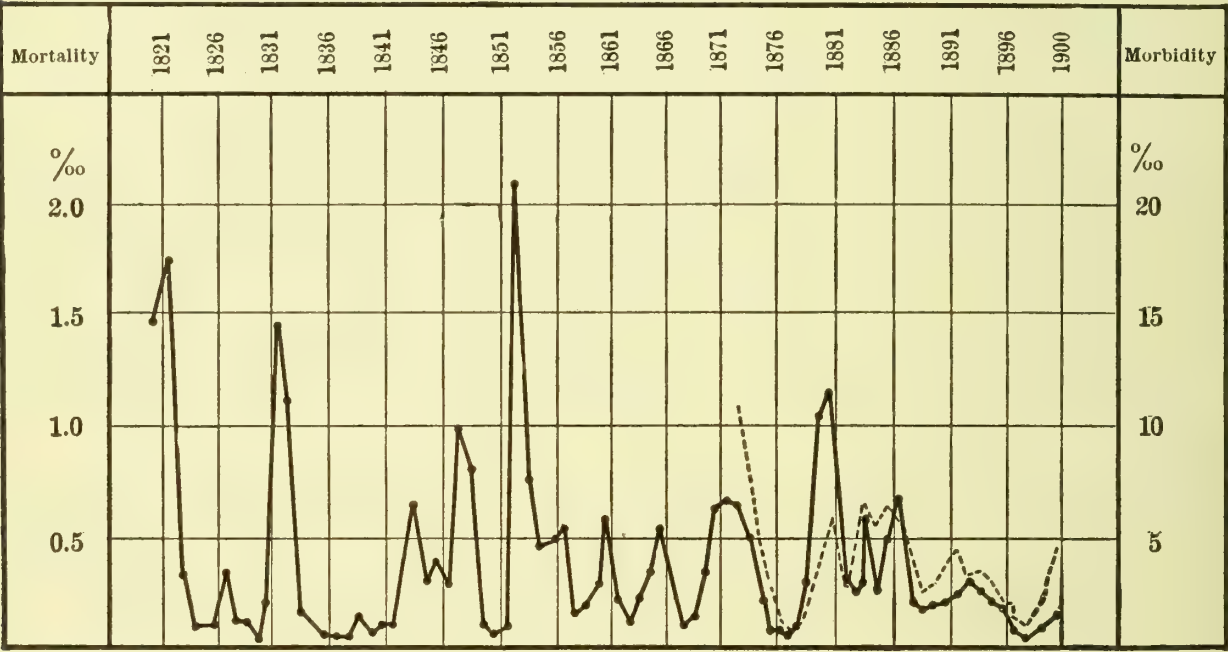


FIG. 23.

an autochthonous condition outside of the human body, are based upon the observation of cases in districts in which for a long time no case of scarlatina has occurred and also in which no cases were imported. However, since we know that, under some circumstances, the transportation of the poison of the disease may occur by means of healthy individuals, certainly by those that have but a mild degree of tonsillitis, in which the patient does not regard himself as sick, these experiences are no longer tenable with the law of unqualified contagion.

Of this poison, which is renewed year after year in thousands of people, and increases, as little is known regarding its nature as of measles. Since the beginning of the bacteriological era there have been many observers who looked with more or less certainty upon the chains of cocci, which were almost always found in the pharynx of scarlatina patients and very often in the blood and the tissues of the cadaver, as the pathogenic agents of scarlet fever. The majority of these observers, similar to Sörenson, are probably of the opinion that it is not a parasite which is identical with the streptococcus pyogenes, but that it is a microbe which morphologically resembles the usual strepto-

coccus and one that possesses a special specific character, the property of producing a particular disease. Up to the present, no examination of the streptococcus found in scarlatina has shown the specific property of the germ. Moreover it has been shown that in all points which can be determined it resembles the streptococcus erysipelatos.¹ In the streptococcus of scarlatinal angina, Hilbert was not even able to determine the property of secreting toxins which Baginsky and Sommerfeld had maintained. The constant occurrence of this microbe in the blood of recent scarlatinal infections (or at the autopsy) could not be demonstrated by Böhm in Baumgarten's Institute, nor by Slawyk in my clinic. Naturally, all tissues were not examined. Perhaps it will be possible by more accurate bacteriologico-biological investigations to solve this question.

[Class recently demonstrated in the secretions of the throat, in the blood and in the desquamating epidermis, a diplococcus which was pathogenic in mice, swine and guinea-pigs.

Baginsky and Sommerfeld have described a streptococcus. Later, Baginsky and Monti showed the presence of streptococci in short and long chains almost constantly associated with other organisms, as pneumococci, staphylococci, and forms of diplococci in smears from the pharynx. The urine, and in two cases the fluid withdrawn by lumbar puncture, contained streptococci. From the autopsy material studied, the streptococcus was isolated in every instance and almost always in pure culture. These observers do not commit themselves in regard to the causal relation of the streptococcus to the disease. The hypothesis that scarlet fever is a streptococcus disease does not receive direct support from recent studies of the blood by Hektoen. This observer made bacteriological examinations during life, especially in regard to general streptococcus infection. He states that streptococci may occasionally be found in the blood in cases of scarlet fever that run a short, mild and uncomplicated course; that streptococci are more frequent in the severe and protracted cases; and that they are not found in some of the fatal cases. Very recently Mallory has demonstrated the presence of very remarkable segmenting bodies in the tissues of cases of scarlet fever.—Ed.]

We are better informed regarding the manner of distribution of the scarlatinal poison than of its nature. Our northern colleagues who have had an opportunity of studying the disease upon isolated islands or in villages situated in the woods in which little communication existed, have been able to supply us with valuable points.² Especially the epidemic in Lommedalen, studied by Johannessen,³ is particularly instructive, because this author had an opportunity of observing the entire population, amounting to 533 persons, in a village near Christiania, so that not even the mildest case of scarlatinal angina could escape him. From these observations, the individual

¹ In 1888 my pupil, S. Lenhartz, succeeded in producing an erysipelatosus affection in mice by means of a streptococcus cultivated from scarlatinal blood. (Jahrb. f. Kinderheilk., Bd. xxviii.)

² Hoff, Erfahrungen auf den Faröerinseln über Scharlach. Quoted by Jürgensen, Scharlach in Nothnagel's Handbuch, iv, 3, 2. Abth., p. 3.

³ Johannessen, Gut abgegrenzte Scharlachepidemie in Lommedalen. Archiv f. Kinderheilk., Bd. vi, 1885.

points of which cannot here be entered upon in detail, it could be seen that nothing but human intercourse, and only this, is capable of distributing scarlet fever. Most frequently it is the mild or not severely affected patients that communicate the disease to susceptible healthy individuals; and the most dangerous transmitters are those adults in whom the disease often exists as an angina (tonsillitis) which is not even accompanied by fever. Thus the entire epidemic, in the previously mentioned lonely Norwegian village, was produced by a servant girl aged twenty-nine who had nursed a scarlet fever patient in Christiania, and being attacked by angina tonsillaris, on the third day of this disease returned to her home situated in the midst of a forest, four hours from Christiania. She was not ill enough to take to bed but was out daily. She spread the contagion to her own and to other families and from these foci the disease was distributed to over 24 families that lived quite distant from one another, attacking in all 67 persons, or 13.9 per cent. of the entire population, in so far as they were not protected by a previous attack of scarlatina (44 cases).

In large cities, in the greatest majority of cases, the first flaring up of an epidemic occurs by infection in the schools. Those attacked take the disease home with them and transmit it. Among the schools, all those places are to be included in which a large number of children are thrown together: therefore, kindergartens, infant institutions, asylums, etc. Children's parties not infrequently give an opportunity for transmitting the disease. In by far the greatest number of all transmissions, the active agent has naturally not yet been recognized as a scarlatina patient, either because the affection is so mild that there is no thought of a severe foundation of the scarcely noticeable throat difficulty or because the patient is only at the onset of the disease. How frequently does it occur that children, on account of sudden illness and vomiting, are sent home from school, are put to bed and develop scarlatina. During this onset of the disease they have had an opportunity of transmitting the malady to their susceptible neighbors. A second category of infection occurs at the termination of the individual disease. After a fortunate recovery from the affection the little patient is looked upon as completely well if he has regained his former strength, appetite and sleep, and no more of the pathological changes can be found in him. The patient, even as regards his own sensations, has recovered, but in spite of this the poison still adheres to him. It is not to be doubted that this is still the case up to the end of the sixth week after the onset of the disease. A child that had completely recovered from scarlatina, at the end of the sixth week, on account of the still existing discharge from the ear, was sent from my scarlatina division in the hospital to the ear department of the Charité. Four days later his neighbor was attacked by scarlatina. Similar experiences in greater numbers may be gathered from the return of children to their own families, that have recovered from scarlet fever in the hospital, even if the proof of a causal connection between a new affection and contagion by means of the convalescent cannot be shown with certainty. Now, the question may even be propounded, whether the sixth week is the final period in which a convalescent is no longer dangerous. Usually the desquamation of the epidermis, which lasts until this time, and may even continue longer, is looked upon as the danger period for infection, and the scales them-

selves are supposed to be the carriers of the poison. This assumption is by no means proven. It is just as likely that the poison is contained in the pharyngeal organs, in the pus from the ear, in the urine, or in other excretions.

In fact, even of the recent scarlatinal case, it is by no means known with certainty regarding the seat of the contagion, whence it disseminates itself and how it leaves the body so that it is capable of entering a second organism. Clinical experiences render it quite likely that the first point is the mucous membrane of the pharyngeal organs, perhaps, also at least at the onset, this is its principal point of reproduction. The transmission appears in quite a number of cases to occur in a fleeting manner, i. e., without direct corporeal contact, kissing, shaking of hands, etc. The expulsion of sprays of saliva from the mouth of the patient in speaking, which is pointed out by Flügge, may be the method of transmission of the infection. Probably more frequently, especially in the case of younger children, the introduction of the finger or other substances which have come in contact with the poison, into the mouth of the healthy brings about the contagion. This mode of transmission is facilitated by the property of the scarlatinal poison of adhering to fomites, such as toys, books, tools, which a scarlatinal patient has used, for some time, also to letters, linen, beds, clothes, etc. Food substances also, in case they are not heated before use, such as cakes, and especially milk, may retain the scarlatinal contagion. That the poison may remain in rooms, on the wall paper, in hallways, and even apparently after thorough disinfection, has been proven by the frequent unfortunate experiences in cases where children have been away from home and upon returning have been taken sick in a carefully cleaned room. The other possibilities, however, also remain open that the poison may still adhere to the body of the apparent convalescent or perhaps may adhere to the nurses or parents that have shown but a slight attack. That a healthy person, and a healthy third person, may be the carriers of a contagion will probably belong to the rarest possibilities, but that this does occur cannot be doubted. Johannessen communicates an unquestionable case which, in my opinion, shows this mode of transmission. It is that of a servant girl whom he himself had treated two years previously for scarlet fever, and who at the time of transmission did not even show a slight angina. It appears, however, that only such persons are capable of transmitting the disease as remain in the immediate vicinity of the patient, as nurses or servants, and who also come in contact with susceptible healthy persons for a prolonged time.

The point at which the poison is taken up on the part of the attacked individual, as has been mentioned, is most frequently the posterior portion of the naso-pharyngeal space and the oral cavity. Besides this, however, the scarlatinal poison has the peculiar property of utilizing interruptions of continuity of the skin as the ports of entrance to the organism. A varicella pustule which has been scratched, a wound upon the penis in a phimosis operation, an accidental tear of the finger, may be the first points of attack of the scarlatinal infection. Puerperal scarlatina also finds its entrance by way of the smaller or larger injuries upon the genitalia, due to childbirth. In such instances, first the wound assumes an unhealthy appearance, the borders show-

ing a smeary or membranous coating, then the surrounding area becomes red, and thence the general cutaneous eruption begins to develop itself. The circumstance that in the coating of the wounds in such cases, especially in pregnant women, streptococci are always found, Sørensen quotes in proof of his assumption that this streptococcus possesses etiological connection with scarlatina. If only the streptococcus were not the principal factor in most of the other puerperal processes even in those in which scarlatina does not come into question at all!

The susceptibility of the human race at this time is limited; perhaps in this connection not all people and races are alike, even individual families appear to possess absolutely no resistance toward scarlet fever. Under certain external influences (the season) the susceptibility may be increased. But everywhere adults are more resistant than children. Scarlatina, in a much narrower sense than in the case of measles, is a disease of childhood. Johannesen saw in Lommedalen 28.1 per cent. of children, 5.1 per cent. of adults, attacked (in the families in which contagion occurred, 36 per cent. of the children and 82 per cent. of the adults remained free). In childhood the susceptibility is greatest between the third and fourth years of life, but remains high, however, up to the tenth year and then declines. Nurslings are much less susceptible, especially in the first half of the first year of life. I have never seen a positive case of scarlatina in a child under six months of age. (A case recently reported by Kroner,¹ in which a child aged seven weeks was said to be attacked by scarlatina, is somewhat doubtful.)

Recovery from the disease in the greatest majority of cases, confers immunity toward new infection, certainly up to the adult age, when the susceptibility becomes lessened of itself. But the protection against scarlatina appears to me to be slighter than in the case of measles. Among 359 cases treated by me in Leipzig, I met with 6 cases that had been treated for scarlatina, by competent physicians that were known to me, and at that only five years previously. Two of the cases were merely attacked by severe angina, while a brother at the same time succumbed to a fatal attack.

The period of incubation of scarlatina is liable to greater variations than any of the other acute exanthemata, but in the main it appears to be a short one. The well-known case communicated by Trousseau²—provided there were no source of error—would show a period of incubation of twenty-four hours, the most usual duration of the period of incubation will be found to be between four and seven days.

PATHOLOGY

The pathological changes occur particularly in the mucous membrane of the pharynx and in the skin. The changes in the kidneys will be described later on.

In the pharynx, in the milder cases, there is a very decided hyperemia of the mucous membrane and a hyperplastic process in the entire adenoid substance. As well in the larger deposits of this tissue, in the pharyngeal and

¹ Deutsche med. Wochenschr., Nr. 51, p. 896.

² Med. Klinik des Hôtel Dieu, 2te. Aufl., German by *Culmann*, Bd. i, p. 98.

palatine tonsils, as everywhere in the separated follicles of the mucous membrane; at the base of the tongue, of the lateral and posterior wall and at the entrance of the pharynx, a distinct increase is noted in the lymph cells filling the fine fibre net. The same condition occurs in the lymph glands in this region belonging to the inframaxillary and retropharyngeal region. The sharp limitation of the inflammatory hyperemia of the mucous membrane of the esophagus and entrance to the larynx, which may still be recognized in the cadaver is noteworthy and characteristic. Particularly in the first-mentioned area, the hyperemia terminates in an abrupt straight line. The upper surface of the mucous membrane is found to be in a catarrhal condition with a mucopurulent exudation, especially upon the surface of the tonsils.

In the severe cases, which terminate fatally in from one to four days, this acute hyperplasia of the lymphatic tissue is often found developed to an enormous extent over the entire body. Not only the peripheral lymph glands upon the neck, those in the axilla and in the inguinal region enlarge, but also those throughout the entire intestinal tract, as well as all the lymph follicles, all Peyer's patches, the mesenteric glands, and even the spleen are enlarged to a similar extent; upon section this latter organ shows medullary swelling, it is pulpy and coarse. New formations of small lymph nodes are found in the liver and in the kidney. The last-mentioned organs in these cases appear markedly hyperemic, here and there small hemorrhages are found, particularly near the surface. According to van den Berg,¹ the blood with but few exceptions shows a hyperleukocytosis which lasts for several weeks and is due to the polynuclear elements. The heart in the rapidly fatal cases is usually flaccid and pale; but also quite firm and markedly contracted left ventricles are noted.

In cases of a slight or medium severe infection, the more locally limited inflammatory disease of the mucous membranes and lymph gland enlargement diminishes in the second half of the first week or in the beginning of the second week, even though, subsequently, in one or the other gland, a more substantive inflammatory process may develop. In very many cases, however, the serious turn which the affection takes occurs in the pharyngeal organs. The simple severe inflammation then changes its character and leads to an inflammatory necrosis of the tissue, by the formation of a coagulated, simultaneously hemorrhagic, exudate. Partly (but usually not to a marked extent) this is found upon the surface of the mucous membrane, between and beneath the epithelium, in the form of thin, often disconnected membranes, partly to a slighter, at other times to a more marked extent, in the tissue of the mucous membrane and in the adenoid layers. But even there this inflammation (in an anatomical sense a true diphtheritic one) does not halt, but attacks the mucous gland layer situated beneath the mucous membrane, as well as the fat and muscular tissue, for example, of the palatine arch and uvula, of the epiglottis and of the larynx, altering everything into a rigid opaque mass, of which the original morphologic composition is no longer discernible. The inevitable result of this "coagulation necrosis" as it has been very aptly designated by Weigert, is the destruction of all

¹ Arch. f. Kinderheilk., Bd. xxv.

affected parts. This inflammatory necrosis also attacks deeper lying organs, especially the lymph glands situated near the pharyngeal parts, where it leads to the development of gangrenous hemorrhagic foci, which again are a source of danger to the surrounding areas, the cellular tissue of the throat. This tissue shows phlegmonous inflammation with widely distributed rigid tissue infiltration, with the formation of gangrenous foci varying in size. In the internal organs, especially the liver, circumscribed diphtheritic foci of slight extent may develop.

It is remarkable that in this diphtheritic, or better—to differentiate the process from genuine diphtheria, with which etiologically it has nothing in common—*diphtheroid inflammation* of the pharyngeal organs, with extremely rare exceptions, in the cases that die during the first days of the disease, even though the adenoid conglomerations are as markedly hyperplastic as possible, nothing is found. The starting point appears to occur mostly upon the fourth day of the disease.

The following case is an illustration of a beginning diphtheroid condition which has just been described.

Swob., Albert, aged ten years, attacked upon June 13, 1888, in the afternoon, with high fever, limited eruption, delirium, unconscious upon the 16th, and died upon the afternoon of the 17th of June.

The pharyngeal parts show a line of demarcation at the velum palatinum downward to the entrance of the esophagus, consisting of a sharp border of a dark bluish-red color. Inside of this area, upon the uvula, fine, hemorrhagic, punctiform regions may be noted. Upon the surface and in the lacuna of the left tonsil there is a muco-purulent coating. A section of the tonsil shows a marked medullary, swollen consistence of a reddish-white color. The same condition is noted upon section of the right tonsil, in its lower half. The upper half, however, shows a sharp demarcation compared with the lower, consisting of a high-graded, dark red discoloration, due to an inflammatory, hemorrhagic infiltration. A stream of water let fall upon it shows that the upper surfaces of the tonsillar swelling in these areas have separated and that a necrotic decomposition is beginning.

This diphtheroid process is combined with a very regular bacteriologic finding which is so constant that we may speak of a relation of the one to the other. Whereas in the first days it is impossible to find microbes in the microscopic sections, even in the markedly swollen tissues—their presence very frequently may be determined bacteriologically—in the diphtheroid areas, great masses of streptococci are found, and not only this, they are found in the spaces of the tonsillar tissue and may even quite often be found in sections in the tissue of the lymph glands.

Regarding the rôle which is to be attributed to the streptococci in this dangerous process, the opinions of those authors who deny an etiological connection between streptococci and the scarlatinal poison are still divided. Some look upon the serious change which occurs in the scarlatinal mucous membrane as the direct action of the previously mentioned microbes, which, already present to a lesser or greater extent in the oral cavity, find opportunity to gain a firm foothold upon the changed mucous membrane areas due to the scarlatinal infection, and, entering the tissue, produce an inflammatory necrosis. Others believe that the scarlet fever diphtheroid is due to the action of the still unknown scarlatinal virus itself in especially susceptible

individuals that have a weak mucous membrane, and only the necrosed tissue itself opens the tract for the massive proliferation of the cocci chains and their entrance into the organism.

I favor the second view in regard to the circumstance that the diphtheroid mucous membrane disease—therefore, the beginning of the tissue necrosis, not the surface exudate!—so commonly holds to a distinct phase of the course of scarlet fever and that streptococci in every case of scarlatina are present in the pharynx, diphtheroid, however, not always taking place. A decision will only be possible after we have learned to recognize the scarlatinal virus with certainty. Practically of great importance, however, is this, that the streptococci after they have found an easy entrance into the organism affected by scarlatina become very potent in regard to the further course of the affection. The opponents of the law of the specificity of the streptococci must also admit that the resistance of the organ to the deleterious effects of the microbes in scarlatina is particularly slight, less than in almost all other diseases. For this reason, streptococcus sepsis plays such an ominous rôle in the prognosis of scarlet fever. At one time this shows itself in the form of severe phlegmonous inflammation of the throat, at other times the coccus infection is transmitted by way of the lymph tracts, again it creeps along the retrotracheal and mediastinal connective tissue tracts, at other times the coccus infection enters a vein and produces secondary pyemic blood disintegration, with multiple, purulent metastases in the most varied parts of the body. Scarlet fever pyemia, deviating from other analogous infections, shows the peculiar character that the joint cavities and the serous membranes are particularly predisposed to purulent deposits. In all cases of this kind we may speak of a proliferation of the streptococci through the entire body and in such quantities, very much greater than the relatively distributed germs which are found in recent scarlatina cases (without diphtheroid) even in the first days of the disease in the blood. The amount of streptococci in the blood, according to the investigations of Slawyk,¹ who worked in my clinic, observing all necessary precautions, in general is parallel to the intensity of the diphtheroid mucous membrane inflammation, even if this is not the only point of entrance for the microbes, but may share this property with other inflammatory mucous membrane diseases, especially of the auditory canal.

Slawyk found the blood, in 15 cases which terminated fatally on the third day of the disease, constantly sterile, only upon the fifth day of the disease the investigated cases showed, and then in decided quantities, streptococci in the blood.

If it is true that streptococci do not produce toxin formation, it must be assumed that the bacteria themselves, by their property of producing inflammation, give rise to the severe, mostly fatal affections. However, we have observed a number of cases in which, in spite of septic fever and of the fact that the other clinical phenomena pointed to sepsis (such as the gradually decreasing power of the heart, the loss of appetite, emaciation, the frequent implication of the sensorium) neither purulent foci in the body nor streptococci in the blood could be determined, therefore, death appeared to be due to

¹ Jahrbuch für Kinderheilkunde, Bd. liii, Heft 5.

a pure septicemia. These were mostly cases in which stubborn and severe otitis media complicated the disease (but without sinus thrombosis or other local infection of neighboring organs). Observations of this kind require further bacteriological study.

The *changes in the skin* in scarlatina require further pathologico-anatomical study. The investigations up to the present do not favor a simple "vasomotor" hyperemia, such as is produced by chemical poisons, but they favor inflammatory processes. Besides marked hyperemia of the papillary body, the vascular nets in the deeper layers of the cutis are greatly dilated and markedly filled with blood, and along the smallest veins narrower or broader streaks of round cells are noted, which cannot be looked upon as anything else than as emigrated leukocytes. With this, the tissue of the cutis and the cells of the rete Malpighi are apparently richer in fluid, as if swollen, this may even be noted in hardened preparations. The fine dark points which we shall learn to recognize in the description of the eruption, apparently lie in the deeper layers of the cutis (third venous net of Spalteholz),¹ whereas the general redness may be ascribed to the papillary body.

SYMPTOMS

Our description shall represent the picture of an ordinary, medium severe attack of scarlatina. It corresponds to a certain type which this acute exanthem possesses, although at the bedside deviations from this type are in the majority.

In rare cases indistinct phenomena, general disturbance in health, often chilliness and the like, may precede the disease for a few days and even for a week, which may be looked upon as symptoms of the period of incubation. Usually, however, the disease begins abruptly with severe symptoms, so that the chronology of the affection may be accurately determined by the hour. The child returns from school in complete health, a quarter of an hour later vomiting occurs and at once high fever appears. Or it has gone to school quite well and there has an attack of nausea, vomiting appears and the disease begins.

The most frequent symptom at the onset is *vomiting*, according to the time at which the last meal has preceded, either remains of nourishment or of mucous fluid, or sometimes even bile-stained masses, are brought up. In younger children diarrhea is readily added and then lasts for a day or two. Even in nurslings, vomiting and diarrhea are the earliest symptoms.

In cases of medium severity the vomiting may be repeated several times during the first hours of the disease and then cease. Immediately following this a general febrile condition appears. In older children, it may be introduced by a true chill, also in younger ones (rarely) although not as an initial symptom; also, inside of the first few hours or first two days, general convulsions occur, which are not always of unfavorable prognosis. A general feeling of malaise, *headache* (also pain in the limbs), lassitude, irritability, pains in the abdomen always rapidly follow. Somewhat later, from twelve to twenty-

¹ Die Vertheilung der Blutgefäße in der Haut. Arch. f. Anat. u. Physiol., 1893.

four hours after the onset the child complains of its throat, of pain in deglutition. In adults, on the contrary, the pain in the throat is frequently the first symptom.

In practice, not infrequently, there is an opportunity of examining the child shortly after the initial vomiting. It is always found with marked fever, but not always is this high at the onset, but varies between 102.2° F. and 103.1° F., but, occasionally, even in moderate cases, the temperature rises at once to 104° F. to 105° F. (in the rectum). The child assumes the recumbent posture itself, and now a febrile condition is noted which lasts from eight to ten days. Even during the first night, febrile unrest, mild delirium appear, while during the day the child is apathetic, sleepy, complains of thirst, burning and pain in the throat, the speech assumes a muffled, throaty character.

Examination of the oral cavity shows a tongue with a white coating, the filiform papillæ are somewhat reddened and the palatine mucous membrane, with a quite sharp line of demarcation toward the hard palate, is markedly reddened, showing distinct small maculæ, the tonsils are swollen and upon their deep reddened surface, not infrequently, reddish, yellowish flakes or striæ may already be noted.

The face sometimes appears bloated, in some cases transversely over the nose a saddle-like redness is noted, which coalesces with the fever redness of the cheeks, whereas the surroundings of the mouth and chin are almost unnaturally sharply demarcated by a conspicuous pallor.

In the course of the first day or in the first half of the second day the characteristic cutaneous eruption appears, usually first upon the trunk, neck, chest or back, also in the gluteal region and then, gradually, in the course of two days, distributes itself to the extremities. The characteristics of this eruption consist in two peculiarities: At the onset it consists of small points distinctly separated from one another, which, in the course of hours or days coalesce, forming a uniform connected mass of a red appearance and, secondly, at the onset it is of a delicate red, rapidly or also slowly, even in the course of several days, assuming a saturated, burning, flaming, fire-red appearance which, therefore, justifies the name of scarlet fever. In all cases that are at all developed, this general redness, no matter how intense and flaming it becomes, attains its development from separated punctiform areas in so far as in the general redness, upon accurate observation, small still darker flakes may be recognized, especially if by means of slight pressure upon the skin the blood is forced away. Primarily the redness upon decreasing pressure always appears first in the original red areas.

Therefore, upon the neck, on the chest, upon the back, upon a delicate white skin, there are first noted delicate rose-red punctiform, from a millet seed to a pin head in size, particularly round, areas situated close together: At a distance a uniform color is presented, and only upon close observation can the individual points be discerned. Soon the entire trunk appears to be covered and now, at the end of the second or the beginning of the third day, upon the inner surface of the arms, the thighs, soon also taking in the outer surface, reaching to the fingers and toes, the same fine redness is noted. The skin at first feels smooth, but with increasing intensity of the redness it

becomes uneven, coarse, something like shagreen leather. The face frequently remains entirely free or only signs of the fine red points are noted upon the temples, the dorsum of the nose or on the outer surface of the cheeks. The region about the mouth and chin invariably remains free. With each succeeding half day the red points coalesce more and more and become darker, upon the third, fourth, sometimes only upon the fifth day, the skin from the throat to the feet shows a condition as if the patient were covered by a scarlet mantle which closely envelops the entire body. In the inguinal region, at the elbow, and at the knee joint, upon the buttocks, upon the inner surface of the thighs, the eruption is usually particularly intense, often showing a bluish-red shade. It is not infrequent, even in cases running a normal course, that in these previously mentioned areas the original red points show a hemorrhagic tendency and are then particularly noticeable.

In not a few cases, particularly upon the abdomen, but even upon the lateral aspect of the thorax, upon the back, upon the lower legs, the dorsum of the hands and feet, over these original spots there appear vesicles the size of a millet seed, filled with a transparent fluid, which later becomes opaque; these are called miliaria, which after a few days dry and form scales. The contents of these vesicles show an alkaline reaction, therefore, do not consist of the secretion of the sweat glands alone. This form of the eruption is called *scarlatina miliaris*, and its appearance is not considered of unfavorable prognosis; in fact, most cases of *scarlatina miliaris* run a favorable course.

Opposed to this—but even this again has exceptions—is another deviation of the exanthem. Upon the third or fourth day in the occasionally slightly uneven, but not particularly raised, eruption, nodules and papules the size of a lentil seed, usually of a deeply stained color, are noted to appear, which are situated at some distance from one another and sometimes produce great itching. In those cases in which the rash has a limited distribution these papules may end the general redness and then show an appearance which simulates urticaria. This form of the exanthem is seen much more frequently in the severer infections.

Upon the dorsum of the hands and feet the skin occasionally swells and becomes glistening, sometimes almost resembling erysipelas.

A peculiar condition is noted in the fully developed exanthem if the finger nail is passed over the red surface, in the entire extent over which the nail has passed a white streak of varying intensity is noted (apparently due to vaso-motor spasm) which only slowly disappears (*raie blanche* of the French).

After the greatest intensity has been reached the eruption remains at its acme for half a day or longer, then it begins to fade and disappears at the end of the first week or the beginning of the second, frequently slight exacerbations being noted in the interval, these usually occurring toward evening. Even before the fading is completed the epidermis begins to peel in many areas, first, usually, upon the neck, and this desquamation continues often for many weeks, even in convalescence. Upon the neck, upon the chest, and in the inguinal region, this desquamation occurs in small flakes or plaques, from the size of the head of a pin to that of a lentil; they are of a white glistening appearance. Upon the buttocks, the thighs, the hands, and feet,

however, large lamellæ, and entire casts of the fingers, or the hands, which may renew themselves several times, may be shed. Finally, after a prolonged period of desquamation, the patient enters upon convalescence with a renewed skin.

Occasionally, in this rapid transformation process of the skin, an improvement in chronic difficulties occurs: Thus, in a case of intense desquamation, I once saw numerous warts covering both hands of a seven-year-old girl disappear without leaving a trace.

Hand in hand with the development of the exanthem the fever proceeds. Simultaneously, or even earlier, often even upon the second or third day it reaches its acme, the absolute height of which in ordinary cases may be quite high, reaching 105° F. or even higher. Usually in a favorable course it does not long remain at this height but soon declines, however, not to fall suddenly and rapidly but quite gradually and slowly, so that in the course of a few days, falling a little each day, normal ranges are reached. Characteristic of an undisturbed defervescence is the fact that after the temperature has begun to decline no increased rises are noted over the previous evening or morning temperatures, whereas in the course of a day the variation between morning

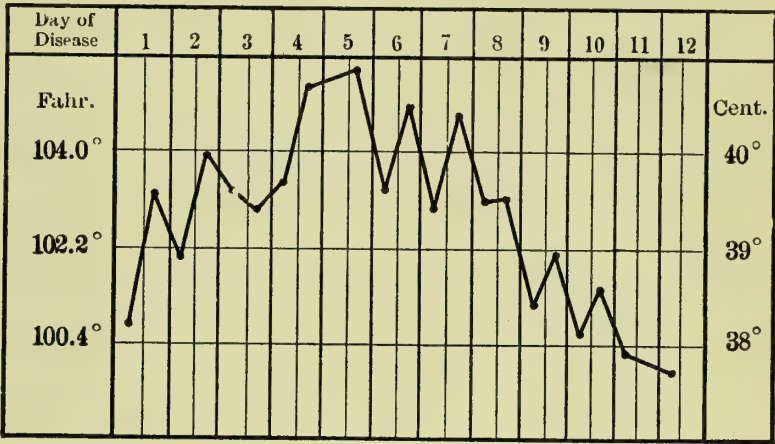


FIG. 24.

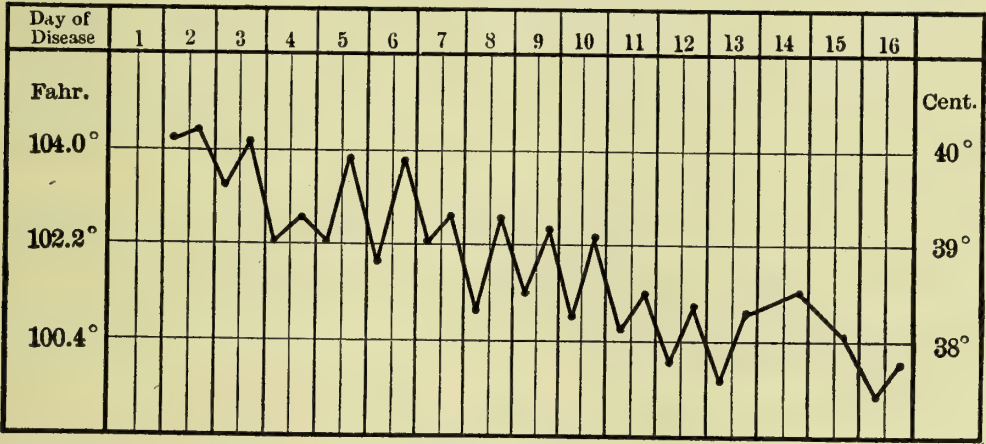


FIG. 25.

and evening still remains. The decline of the fever may be likened to a staircase which gradually leads downward.

The following temperature charts (Figs. 24 and 25) are examples of simple, uncomplicated scarlatina (rectal temperatures). In the first instance the acme was reached somewhat late, the defervescence being somewhat more marked, in the second case the acme is noted on the second day, the defervescence being slow and gradual. Both cases entered upon an undisturbed convalescence without complications.

The *pulse* in scarlatina shows peculiarities in being very rapid, greater in proportion to the height of the temperature and age of the patient than in other diseases. This is also true of the uncomplicated cases and it cannot even be said that this symptom is more markedly developed in the severer infections. In children from five to six years of age, in the first few days, even in mild cases with a rectal temperature of 103° F., from 150 to 170 pulse beats per minute, with a temperature of 102° F., 132 per minute, with a temperature of 100.5° F., 124 per minute, etc. In a girl aged seven (medium severe case), I found, with a temperature of 101° F., 150 beats per minute. With higher temperatures, pulse beats of nearly 200 per minute can be counted (for example, in a girl aged five with a temperature of 104° F.), without the prognosis necessarily being unfavorable. Nor does the pulse rise much higher in the very severe, fatal cases with excessive high temperatures. In a boy aged five, with a temperature of 107.8° F. I noted 196 beats per minute. In a case which terminated fatally in a girl aged two, with a temperature of 104° F., 204 beats per minute. From this symptom it may be quite properly concluded that the scarlatinal poison, more decidedly than other infectious products, has a direct action upon the cardiac nerves which increase the heart beat. The condition of the pulse in the first days is sometimes rapid, usually, however, it is soft, not dicrotic. Some sphygmographic tracings appear to favor the view that the vaso-motors of the peripheral vessels are in a certain spasmodic condition, which is also indicated by the previously-described "white streak." While the exanthem is reaching its full development, the inflammatory affection of the larynx and the oral cavity increases. The tonsils become more swollen, the muco-purulent or fibrinous flaky deposits upon their surfaces become distinct, but if they were previously present, they now increase and enlarge, the lymph glands at the angle of the lower jaw enlarge and become painful, the tongue loses its white coating and the superficial layer is denuded of its epithelium so that the tongue looks red and smooth, but the papillæ stand out prominently above the surface like red warts. If the child protrudes the tip of the tongue between the lips it resembles a strawberry. A tendency to dryness of the tongue readily occurs upon the days when high fever is present.

With the fading of the eruption and the onset of defervescence the mucous membrane affection improves, the yellow spots upon the tonsils disappear; the tonsils are less swollen, the glands decline in size, the tongue regains its normal epithelial covering.

Other decided deviations on the part of the internal organs are not noted during the acme of simple scarlatina. The respiratory apparatus is hardly affected, at most there may be a slight tracheo-bronchitis. The urine shows the characters of febrile urine, it is scant, high colored and, with an intense fever, may show small amounts of albumin and some few hyaline casts; this disappears as the fever declines. A slight increase in diacetic acid is often noted, the diazo-reaction is negative. The spleen is very commonly enlarged, which may be shown by percussion but may also be noted upon palpation.

Anorexia is present during the entire course of the fever, but there is great thirst. After the preliminary diarrhea the bowels are usually constipated. With defervescence and a decline in the eruption, there is a return

of the normal epithelial coating of the tongue, appetite returns, and the digestive apparatus begins to functionate normally.

Toward the middle of the second week the pathological disturbances have almost disappeared, only the skin which has been deeply affected still requires a longer time to regenerate itself and to return to its normal condition.

Strength and subjective well being usually return rapidly. Only the impossibility to foresee the later implication of the kidney influences the careful physician, even in these cases, to keep the patient in bed at least till the end of the third week and to watch him carefully.

VARIATIONS FROM THE COMMON TYPE

We shall now devote our attention to the *manifold deviations* from the just described simple course, a review of them being only possible in that the individual course is viewed particularly in regard to the organic disturbances which become prominent. Naturally, it must not be forgotten that in each special case these deviations are not always so distinctly separated from one another as they are in text-book descriptions, the disturbances commonly combining, crossing or following one another.

In scarlatina, which quite properly is so much feared, we also note *mild* and *very mild affections*. In such cases all symptoms of the disease are but slightly developed and of a very benign character. At the onset vomiting and headache may be present but the pharyngeal affection is only noted by slight swelling and reddening, the fever rises to a moderate height for but a short time and may sometimes show a purely afebrile character, in other cases only subfebrile rises occur, the temperature only rising to 101.5° F. and rapidly declining, the fever may even sometimes be absent entirely. The eruption consists in a uniform reddening of a pale rose color, distributed over the entire body, which may in individual areas, upon the neck, upon the buttocks, show a slightly raised character or this may be absent entirely; or the eruption may only be found in individual areas, for example, upon the groins, at the flexures of the knee, upon the neck or upon the back, being even fleeting here or remaining for several days. The diagnosis in these cases can only be made with certainty upon a careful observation of the entire body and only then by the aid of such knowledge as that other children in the house have been attacked in a well developed manner or in the presence of an epidemic. Sometimes the eruption is well marked, but only upon one part of the body, for example upon the legs, at other times days pass until the rash distributes itself from one part of the body to another.

The *rudimentary cases* must not be placed in the same category with these mild cases. These at the onset may appear quite mild and many of them even remain so, but very frequently in the wake of these apparently harmless disturbances is a late renal affection. The rudimentary character is shown in that the infection appears in the form of an angina frequently severe, and accompanied by fever, and without any eruption. Especially adults, but also older and younger children, for example, also those that have previously had an attack of scarlatina and have been exposed anew to a marked family endemic are not infrequently attacked in this manner. There is marked fever,

often also vomiting and headache, a pharyngeal inflammation, with enlargement of the tonsils and the adjacent lymph glands, often with flaky deposits lasting for some days and then rapidly disappearing and healing without serious consequences, so that the patients appear cured in the course of a few days. Frequently the sharply defined border of the dusky, sometimes even flaky, redness about the hard palate shows the true character of the affection, at other times attention is directed to the condition by an unusual implication of the nasal mucous membrane, in which there is thin mucoid corrosive fluid which collects about the openings of the nose and the upper lip, producing excoriation; often even these symptoms are absent in the clinical picture and it is thought that an ordinary tonsillitis is present, provided no new unquestioned cases of scarlatina are brought about by such cases or unless an edema develops two or three weeks later and shows the true nature of this angina.

Compared to the interesting pictures of the disease which we have just described, the affection shows itself sometimes in a dreadful, almost demoniacal form, when it appears as a so-called *scarlatina fulminans*, *scarlatina gravissima*, *intoxication form of scarlatina*. Almost like lightning, or like a poisoned arrow, in the midst of blooming health, and in the course of a few hours, destruction has been wrought by this property of the scarlatinal poison, which, in common with some other infections (variola, cholera, bubonic plague, etc.), and in some epidemics, is characterized by a great number of such rapidly fatal cases. In the severest cases the affection up to the time of death lasts from thirty to thirty-six hours. Such cases are fortunately very rare, I have only seen two or three among many hundreds of cases. The severest injury to the nervous system on the one hand, to the heart on the other, often without the appearance of the usual characteristic symptoms, destroys life. The following observation is an example:

Girl aged three and a half years, taken ill with vomiting, in the afternoon of December 6, 1875. An evening temperature of 102.6° F., pulse 176. December 7th, early in the morning, a temperature of 104.9° F., pulse 218, unconscious at noon. At 2.30 in the afternoon I saw the child. There was complete coma, pallor and wide and unreacting pupils. Upon the body an erythema, no characteristic eruption was noted (a brother aged eight simultaneously had a characteristic scarlatina). Temperature 108° F., pulse could not be felt, 196 cardiac contractions. A bath at 68° F. for fifteen minutes, with ice water affusions, followed by enveloping in woolen covers was ordered. Pupils then reacted somewhat but no signs of returning consciousness. Four o'clock in the afternoon, temperature 102.9° F., 108 cardiac contractions. Bath at 77° F., followed by almost no reaction; soon afterward death occurred. The entire affection lasted twenty-eight hours.

By far the greatest number of the cases of this group last longer, from three to four days, until death occurs which, according to my experience, cannot be prevented. The onset of the disease may be fulminant, characterized by very severe and almost continuous vomiting and retching, or also by spasms, and even general convulsions. At other times these serious symptoms only develop upon the second day after a moderate onset; above all, they consist of an unusually severe implication on the part of the nervous system. Sometimes violent, at other times quiet but continued delirium or maniacal irritability introduce the drama and rapidly lead to a profound implication

of the sensorium, to complete bewilderment or deep coma. The face usually assumes a peculiar disturbed, frightened expression. This severe implication is usually paired with great restlessness of the motor organs; it appears as if an internal fear compels the little sufferer to a continuous change of position of the body and thus the patient is often found with the head hanging out of bed, lying across the bed or in a complete inverted position in the bed. Very frequently the respiration is loud, resembling that of a person who has run for a long time or it may be that form of respiration which occurs in diabetic coma, deep, long-drawn and difficult. The appearance of the rash varies greatly. The face is sometimes peculiarly streaked, red, white, pale about the mouth, sometimes there are red streaks upon the cheek, and temple, sometimes dark disseminated, papulous eruptions may be seen, the face as well as the trunk showing a bluish marbling, and only toward the end of life does the rash become more distinct. In other cases, on the contrary, a very rapidly developing intense eruption is noted, which very soon takes on a deep, dark, cyanotic discoloration. In one of my recent cases, in a child aged one year and a half the entire skin of the body was covered by dark blue maculæ, varying in size from a lentil to a silver dollar, which did not disappear upon pressure, while only in some few areas were they smaller, showing a more elevated appearance. The child was not placed in the scarlet fever division of the hospital as its disease was looked upon as a "septic" skin eruption. The pharynx is sometimes but slightly affected, at other times it is markedly implicated, reddened and swollen. The tongue is dry, red, fuliginous, the breath distributes a sweet smell resembling acetone. In the urine a marked diazo-reaction is present, occasionally moderate amounts of albumin and hyalin casts may be noted. The urine as well as the feces are voided involuntarily; the stools show for the most part a diarrheic character.

The fever is high from the onset or at least from the second day on, not infrequently it is excessive. The pulse becomes exceedingly rapid, often being irregular. Acute dilatation may be recognized in the heart, and the weakness of this organ is the immediate cause of a rapid, fatal termination. In another series of cases this does not occur in such a stormy manner as has just been described, but death takes place unexpectedly by a rapidly appearing cardiac collapse. In such cases there is also high fever, delirium, marked eruption, rapid pulse, but in the interval the child shows freer moments, takes nourishment, being less excitable and more quiet, until suddenly, with high fever, occasionally with slight twitchings (once I saw these twitchings occurring bilaterally), death comes on quickly. In cases of this kind the total duration of the disease is from three to four days.

In a third category of these severest cases, the infection lasts longer, up to six, seven, even to eight or nine days. To the severe general symptoms an extremely high-graded implication of the pharyngeal region is superadded. Whereas the nervous system is not so markedly affected, so that consciousness toward the end of life, even though disturbed, is not completely lost, there rapidly occur difficulties in deglutition and respiration, a true "narrowing of the fauces," due to a high-graded swelling of the entire naso-pharyngeal ring. Speech is throaty, can scarcely be understood, respiration is stertorous, the head and neck are held stiff, somewhat posteriorly, the entire neck being rigid

and immovable. Inspection of the throat shows marked swelling at the base of the tongue, the tonsils, of the palatine arches and of the uvula, so that these structures appear as if joined, and from the fourth or the fifth day on a board-like swelling in the region of both angles of the jaw is added which distributes itself rapidly around the inferior maxilla and, meeting the swelling

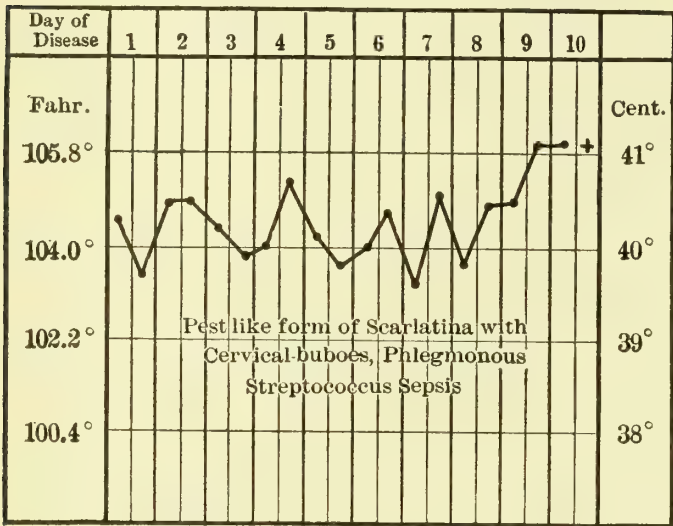


FIG. 26.

coming from the opposite side, takes in the entire upper region of the throat so that these structures appear to be girdled with rigid armor, rendering movement entirely impossible. This swelling is due to a phlegmonous condition of the connective tissue of the throat in the region of the rapidly infected and gangrenous lymph glands coming from the pharynx. If children remain alive up to the beginning of the second week marked destruction of the organs of the throat, which have been

subject to this diphtheroid condition, will take place and a flooding of the entire blood with streptococci with subsequent pyemic suppuration will develop. A severe, usually continuous, fever, accompanies this process which already belongs to the realm of sepsis. The course of such a case is shown by the following temperature curve (Fig. 26).

These forms of the disease, with their rapidly developing buboes about the throat, with subsequent phlegmons and widely distributed tissue necrosis may readily be designated as simulating the plague.

They form the transition to *scarlatinal diphtheroid*, the second variety of severe *scarlatinal infection*, the more or less prominent predominance of the condition giving the character to the scarlatinal epidemic. In this variety, disease of the pharyngeal structures and the adjacent organs is most pronounced in the pathologic process and only by this means do secondary general disturbances occur which again may bring about a fatal change in the disease, but then no longer being part of the original scarlatinal process but to a great extent being of a septic nature.

The pathologico-anatomical process which in this variety of scarlatinal infection attacks the pharyngeal organs has been accurately described previously in this article. It need only be repeated that it consists in a peculiar combination of inflammation and necrosis, in which the latter must infallibly follow the former provided a coagulable exudate is deposited in the tissues of the affected organ. This occurs in scarlatinal diphtheroid to a greater or to a lesser extent.

The disease frequently is accompanied from the onset with high fever and marked swelling of the pharyngeal parts, as well as superficial deposits upon the mucous membrane of the palatine tonsils. In other cases the first days may run a course without any symptoms pointing to the threatening danger.

Besides the other symptoms which may be completely or irregularly developed, thus, the fever, the nervous disturbances, the cutaneous eruption, there is usually found a sharply circumscribed swelling and reddening of the mucous membrane of the palate and pharynx. With the full development of the eruption the fever begins to decline from its acme. A regular course appears to occur. The first sign that denotes disturbance is usually the condition of the temperature. Upon the morning of the fourth or fifth day of the disease the gradual drop in the temperature which has already begun is interrupted; either the morning remission or the evening exacerbation is greater than the day previously and from this time on the regular declining course of the fever ceases and the course becomes atypical. As the observation of this slight alteration in the temperature course is important, in prognosis as well as in treatment, I shall show some examples of this course in the temperature, with corresponding remarks. The underscored portions in the temperature curve indicate the change in the course of the disease.

The observation of the pharyngeal parts at this time does not always indicate the region in which the danger threatens, for which the temperature gives the signal of alarm; especially in little children, in whom the investigation of the pharyngeal areas is often difficult there is noted for the most part only a conspicuous increased formation of a thick tough mucus which covers all parts, rendering an opinion regarding the nature of the beginning changes even more difficult. In older patients it may be noted how the coating upon the tonsils increases, or also in cases in which no superficial deposits are present it may be seen how a slight yellowish or grayish-yellow discoloration occurs in the tonsillar tumor, especially in its lateral aspect, particularly in the spaces between the palatine arches; or a hemorrhagic swelling of the lower portion of the uvula, of the anterior surface of the palatine arch or

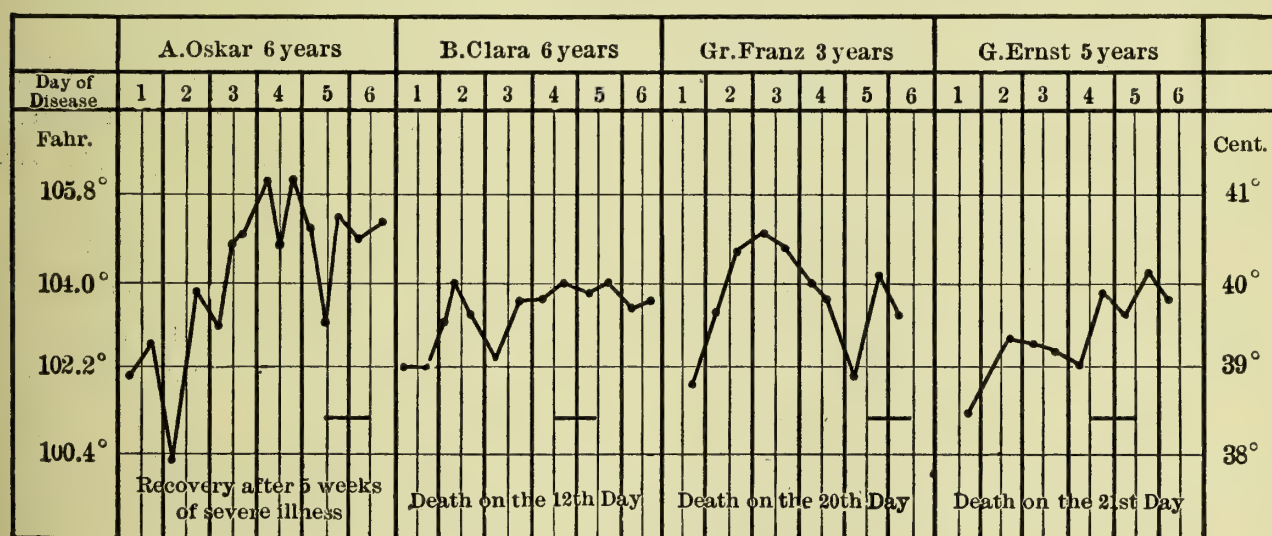


FIG. 27.

similar conditions. Simultaneously with this a flow from the nose occurs, which does not, especially at first, produce anxiety. A thin, stale or even somewhat decomposed, yellowish-red fluid comes from one or both nasal openings and leads usually quite rapidly to an excoriation of the nasal openings or the upper lip. These excoriated areas shows a lardy or dirty gray deposit. At the angle of the mouth small fissures appear (partly due to the forcible

opening of the mouth, but even without this), which soon show a similar coating. Finally, there is added swelling of the lymph glands, first those of the angle of the lower jaw then also the neighboring groups, in the upper triangle of the throat, under the sterno-cleido mastoid. These increase rapidly from day to day, from the size of a bean to the size of a hazelnut, or even attaining the size of a pigeon egg; they are painful to the touch. At first they are movable, soon, however, they appear in the underlying tissues, forming conglomerations of tumors.

Now the difficulty increases from day to day. The tongue becomes dry, the fever hovers around decided heights, the pharyngeal parts swell more markedly or—in the severest cases, those previously mentioned as resembling bubonic plague—in a brief period, in a night, they change into a leather-like, brownish-yellow dead tissue. In ordinary cases the discoloration primarily attacks circumscribed areas and rapidly produces tissue necrosis. After the end of the first week a part of the tonsil, the lower portion of the uvula or also a portion of the velum of the palate may be destroyed and be changed into an ulcer covered with necrotic masses. This is not only the case in visible parts but is not even infrequent upon the posterior surface of the velum of the palate. The diphtheroid has established itself about the choana, about the arch of the pharynx and is the cause of the ichorous flow from the nose. After existing for scarcely a week, as the result of these diphtheroid destructions, it may be noted sometimes even suddenly that a deep hole has formed in the anterior palatine arch, often circular or punched-out in appearance, in the depth of which the partly destroyed tonsil is found; at other times there is a deep fissure in the velum of the palate, which under some circumstances causes a fall of the entire palate upon the uvula, or upon the base of the tongue, at other times a separation of the uvula and the like. These destructions are always accompanied by a particularly profuse excretion of mucus from all the diphtheroid portions of the neighboring mucous glands. In some cases there is added a severe abscess inflammation of the entire oral mucous membrane accompanied by marked salivation; deep ulcers form upon the tongue, the lips swell enormously, are traversed by bloody fissures and disfigure the entire face.

Not infrequently does the diphtheroid inflammation attack the larynx, forming a rigid infiltrate of the ventricular bands and of the subglottal mucous membrane folds as well as numerous small discontinued desquamated deposits upon the surface of the mucous membrane. Both together then lead to stenosis of the larynx, which clinically is similar to true laryngeal diphtheria, giving rise to the symptoms of croup and rendering tracheotomy necessary, which, in fact, only rarely avails to save the threatened life. If then the function of the velum of the palate is hindered, either by rigid swelling or by destruction, a condition resembling paralysis appears; there is nasal speech, regurgitation of fluid through the nose, symptoms which readily lead the inexperienced physician to the erroneous conclusion that he is dealing with true diphtheria.

Although the local signs may be well developed and distributed, they but very rarely cause the tragical termination of these cases. It rarely occurs that the destruction invades the tissue so deeply that a larger pharyngeal artery

is eroded and a fatal hemorrhage occurs; this is an extraordinarily rare development. In the main, even these deep losses of substance heal surprisingly rapidly if the organism is able to recover from the disease. The individual is particularly threatened by way of the glands and the blood vessels.

In the chapter upon pathological anatomy it was explicitly stated that this danger consists in the entrance of streptococci which produce inflammation and suppuration in the tissues and in the blood. There the various ways were described by which this occurs. The organism of the scarlet fever patient responds to this invasion in numerous regions by the appearance of hemorrhagic and purulent inflammations, the extent and number of which depend upon the nature of the entrance and possibly also upon the intensity of the original scarlatinal fever process.

A benign consequence of streptococcus infection consists in a more or less extended swelling of the lymphatics of the lower jaw and neck and the transition in one or the other gland into simple suppuration and abscess formation. Unilaterally or bilaterally upon the neck a circumscribed painful swelling appears, sometimes at the angle of the lower jaw, at other times lower down and more posteriorly, occasionally upon the sterno-cleido mastoid, and in these cases it is usually combined with a transitory stiffness of the head and neck, and with a remittent febrile temperature. Without rupturing, the tumor may recede after existing for weeks, or very frequently in the first, in the second or even in the third week, a deep-seated and later more superficial fluctuation appears, the skin becomes red, tumefies and ruptures in case it has not been incised previously, and pus is discharged.

Frequently suppuration does not occur but dry necrosis takes place. One gland after another enlarges, with continued high temperature, until tumors the size of a walnut and larger develop; the surrounding connective tissue becomes tough, and in the entire region there is a board-like infiltration, individual areas of the skin are discolored, becoming dark blue and then showing gangrenous decomposition; if these parts are incised with the hope of finding pus, a dry, almost cheesy tissue of a grayish-red color is met with that shows the distinct characteristics of gangrenous substance. It is fortunate if by means of a profuse suppuration in the surrounding tissues these dead masses are desquamated and discharged. Much more commonly even these show a gangrenous decomposition and upon both sides of the neck after prolonged fever, markedly distributed, deep losses of substance are noted, the carotid being seen to pulsate at the base, and in some instances even the wall of this vessel has become eroded and a fatal hemorrhage has terminated life; however, death usually takes place without this complication, due to the exhausting fever and the septic consumption. Frequently the local diphtheroid process takes place in the ears as well as in the nose and in the conjunctiva and before death relieves the child both eyes may be totally destroyed due to the inflammatory necrosis.

Again, in other cases the infection runs its course without such conspicuous symptoms but is no less threatening. Slowly the purulent infiltration creeps along the trachea, in the glands, and the neighboring connective tissue, invading deeply and, finding entrance into the thoracic space, it leads to purulent mediastinitis, to which often weeks later a large ichorous empyema or

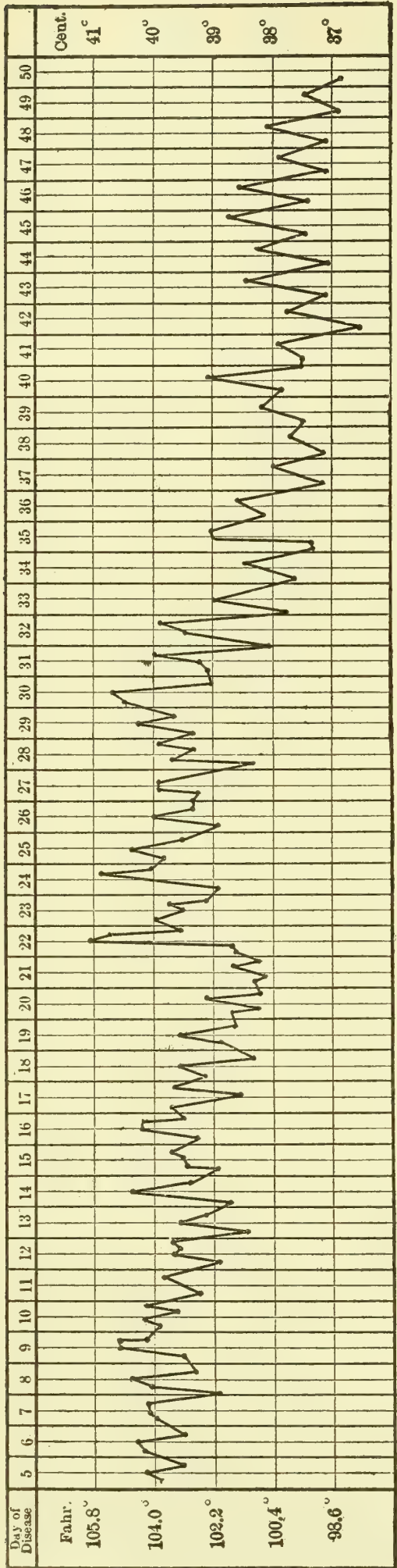


Fig. 28.

a pericarditis is added. To what tortuous tracts this latter fatal affection may lead I have observed twice, in cases in which a purulent meningitis caused the fatal termination, that this had not originated from the nose or the ears but was primarily of a spinal nature, thence having ascended to the brain. In the previously described manner a posterior mediastinitis had taken place, from which a purulent right-sided pleuritis had originated, and thence the suppuration passed through the intercostal nerves, and traversed the intervertebral foramen, thus reaching the spinal cord cavity.

Probably some general purulent cases of peritonitis which are met with in connection with scarlet fever develop in the manner indicated here, by continuity. But just here it may be mentioned that occasionally also *appendicitis* may precede. I have noted the appearance of this disease a few times in the course of scarlatina; a similar relation of conditions has lately been noted between purulent typhlitis (*appendicitis*) with purulent inflammations of the tonsils, the same genetic connection existing.

If these serious changes which have just been described regarding purulent infection remain local and its distribution is limited to the neighboring lymph glands and lymph spaces in the connective tissue, in another series of cases it arises by means of metastasis in areas quite removed from one another, provided streptococci in larger numbers find their way into the blood. The great number of these organisms in the blood can always be shown by bacteriologic investigation. In connection with Bahrdt I published the first case of this kind in which the mere microscopic examination of the blood and of the products of the purulent metastasis showed the general proliferation of the microbes through the entire organism. The way in which this rupture occurs has been directly shown in

individual cases to be due to an original diphtheroid affection of the pharyngeal passages, a septic, inflamed and thrombosed vein being near by in which a septic decomposition of the clogged coagula has occurred. Here by means of continued, usually high, fever, in which, however, chills occur in all possible parts of the body, in the subcutaneous tissue, in the muscles, the kidneys and in other internal organs, smaller and larger abscesses develop: a true pyemia. The joints and serous membranes, especially the pericardium, are by far most frequently affected by this scarlatinal pyemia. The joints in large numbers, the small as well as the large joints, are then subject to purulent infection. The knee joints, the elbow joints, the wrist joints, on one or both sides, especially also frequently the finger joints, enlarge so that there is marked pain upon touch, the patients who are usually almost comatose in this condition manifest the pain by loud cries. The cutaneous covering is reddened in a wide area above and below, swelling in a manner sometimes resembling erysipelas. It is terrible to see how such joints are completely destroyed in a few days, so that upon careful examination with careful movement, the completely destroyed cartilage is felt detached from the bared ends of the bones.

But even with these catastrophes the list of lesions which may arise from scarlatinal diphtheroid is not yet exhausted. The distribution of the local mucous membrane disease has not yet been mentioned or but briefly indicated, which still contains a quiver full of dangerous arrows: *disease of the ear*. This is a very frequent complication of scarlatina. In the hospital I noted it in 27.4 per cent. of all admitted cases (393 patients in the years 1894 to 1897). In the usual manner, by way of the Eustachian tube, the severe mucous membrane affection maintains its character in the pharyngeal cavity, showing a tendency to inflammatory necrosis of the mucous membrane and neighboring bones. The milder forms of otitis media lead to simple perforation of the tympanic membrane, whether this occurs naturally or artificially, terminating in slow recovery with profuse suppuration. Very often, however, this does not terminate the condition; in spite of sufficient opportunity for the pus to flow off, the inflammatory necrotic affection continues into the antrum and to the cells of the mastoid process, in which the osseous tissue itself is implicated and changed into an ichorous necrotic inflammation. From here the infectious process finds its way to the sinus or to the meninges. And in this manner either a general blood affection, a pyemia, is produced, or, by absorption of the poison from the ear, a fatal septemia or a purulent meningitis leads to the lethal termination.

The scarlatinal otitis just described, in its severer forms, is always accompanied by marked and tenacious fever, which even with proper treatment may last for weeks and lead to a severe consumption of bodily strength, so that then only slightly increased disturbance is sufficient to entirely obliterate the remaining feeble strength. Persistent unrest at night, insomnia, delirium, usually a high grade of anorexia, diarrhea and bronchitis belong to the complications which increase the ear difficulty.

The temperature curve (Fig. 28) on page 384 shows a picture of the long-continued condition occurring in the child as the result of diphtheroid and severe otitis, until finally recovery took place.

In this case the appearance of the exanthem was delayed, appearing upon the fourth day and being but little characterized; only upon the eleventh day was there marked swelling and redness of the tonsils with a deposit upon their surface. With a rise of temperature, upon the fourteenth day of the disease the otitis media became prominent. Upon the sixteenth day a high grade of edema was present in the region of the right mastoid process, and in operation upon the seventeenth day the bone was found discolored to a great extent and necrotic, the antrum being filled with granulations and discharging ichorous pus. Slowly and gradually the desquamation of the necrotic osseous tissue took place.

Upon the twenty-second day of the disease there was a sudden exacerbation of the condition with a severe chill. Now the sinus transversus was exposed; puncture, however, did not show the presence of pus. The internal jugular vein was tied with a hook upon the right side to prevent the entrance of septic products from the ichorous ear.

In spite of the continuation of the irregular septic fever until the fifth week of the disease, gradual improvement occurred in the osseous wound. Finally, complete recovery was still further interrupted by a spasmodic attack upon the forty-second and forty-fifth days of the disease which, however, left no deleterious consequences. Ultimately hearing in the right ear returned and was quite good.

At the end of the twelfth week the little patient visited me in my office. The wound in the ear had healed.

In cases of this kind the help of a skillful ear specialist is required, as delay and temporizing is not in place in these severe forms of scarlatinal otitis, in which every day may bring about a serious condition, but the diagnosis must be followed in these cases by an immediate life-saving operation. It is a mistake to dread "interference with the natural process of healing," for this is as good as impossible or represents but an exceptionally fortunate termination. Usually the case runs on as in the following instance when an operation was attempted:

Boy aged thirteen and one half years was taken ill upon December 13th, with a medium severe attack of scarlet fever. Deïervescence occurred about December 20th, and upon December 21st there was an exacerbation and the development of otitis media. In spite of the appearance of the tympanic membrane and the auditory canal denoting trouble, the posterior wall swelling out and even granulation formations occurring, neither the family physician nor the specialist who was called in consultation could conclude to operate upon the mastoid process. In the beginning of January the fever became higher, strength declined more and more and now another ear specialist was called in, who immediately opened the mastoid process and found the entire bone completely softened, and all of its cells filled with pus. Following operation, there was general improvement and decline of fever. But even upon January 3d, there was severe pain in the splenic region, followed by a septic peritonitis, jaundice, and death upon January 5th.

Probably even before the final opening of the pyogenic focus, sinus thrombosis and septic splenic infarct had occurred.

But even without such fulminant phenomena having preceded, we are often surprised by the consequences of an insidious and treacherous disease of the tympanic cavity and of the antrum.

I recently saw an instance of this kind. Upon July 2d, a girl aged twelve years was attacked by scarlet fever, which appeared to run a mild course, so that only on account of the great anxiety of the parents regular visits were continued up to the third week. Upon July 19th, an otitis media began to develop, paracentesis being performed a few days later. Upon July 25th, the mastoid process was moderately painful, but as no fever had developed it was, nevertheless, advised to open the bone. The

operation took place upon July 27th, and great quantities of thick yellow pus were discharged. Upon July 28th, pain in the back, and in the course of the day headache, eleven o'clock in the evening temperature of 104° F., pulse 160. During the next few hours great unrest, rigidity of the muscles of the neck; death upon July 29th, at a quarter past one o'clock in the morning.

In this instance, in a very rapid manner and in an originally very mild case of inflammation of the middle ear, a fulminant meningitis occurred.

In several instances in which there was an otitis media with an apparently good flow of pus, a continued fever was present which could not be explained and in which it was advised to open the mastoid process, in spite of the fact that no swelling of its coverings could be determined and only slight pain upon pressure and the swelling of a lymph gland lying behind the ear pointed to its implication. Invariably, pus and granulations were found in the cells. The fever disappeared and recovery occurred. In cases of this kind, naturally, the opinion of a specialist who has been called in consultation must be considered and he must be supported if he decides in favor of an operation. Instances like those just described rather incline us to take upon ourselves the reproach of polypragmaty than to be guilty of omitting an operation which perhaps might save life.

Scarlatinal Rheumatism.—Much less serious are those irregularities in the course of scarlatina, due to swelling of the joints, which is usually designated by the name of *scarlatinal rheumatism*. This must not be confounded with the previously-mentioned joint affection which almost always is of an unfavorable prognosis.

Scarlatinal rheumatism is not a very frequent complication. I noted the condition 29 times in 358 cases, therefore, in 8 per cent. In my Children's Hospital it was found in 6.7 per cent. of the cases. This proportion allows of the conclusion that the affection is not in immediate connection with the scarlatinal poison but is due to special auxiliary causes. The pathogenesis is not accurately understood, only this much is certain that this multiple joint affection occurs in no other infectious disease as frequently as in scarlatina (acute articular rheumatism naturally excepted).

Clinically, the affection resembles acute articular rheumatism in many respects, but in the main it is more transient in character and of briefer duration than acute polyarthrititis.

In rare cases the condition may be noted upon the first day of the disease; not only as a general muscular pain, but with distinct localization, for example, in the feet. As a rule, it occurs during the second half of the first or the first half of the second week, therefore, in the period between the fifth and the twelfth days of the disease. The large as well as the small joints of the extremities are affected. The vertebra, the jaw, etc., I have never seen implicated. Scarlatinal rheumatism appears to have a special preference for the wrist joints, and also the finger joints are not infrequently attacked. But the legs are by no means spared, the knee joint, the ankle joint, sometimes the joints of the toes and even the hip joints are attacked. Occasionally the affection is only limited to a pair of joints, for example, both knee joints, both wrist joints. Sometimes the affection wanders from one place to another, similar to the condition in primary articular rheumatism.

The local symptoms are quite similar to those in acute rheumatic fever. Occasionally there is no swelling or redness in the region of the joints, and pain upon pressure and pain upon spontaneous movements—but this may occur with great severity—show the implication of the joints, sometimes, however, there is marked periarticular swelling and redness or a distinct effusion into the joint may be noted. Occasionally I found that the entire skin of the feet or the hands was edematous, and once I observed, during an unusually prolonged attack of scarlatinal rheumatism lasting ten days, the appearance of a general (vaso-motor?) anasarca without any signs of a nephritis. The cutaneous edema disappeared simultaneously with the rheumatism.

The duration of the complication is almost always brief, limited to a few days (three to five). In how far the antirheumatic treatment which was employed by me may have caused this cannot be determined with certainty. Some few cases that I saw during the early periods of my practice, before the action of salicylic acid was discovered, ran a similar brief course to those that were treated.

A remarkable fact is that the *heart* is implicated in a like manner to that occurring in acute articular rheumatism, regardless of whether arthritic pains appear or not.

As a rule, these *endocarditic processes* are of a *benign* nature. They must be entirely separated from malignant affections occurring by way of metastasis (similar to the analogous joint affection), particularly from those due to the diphtheroid affection of the pharyngeal organs and cervical lymphatics which preferably attacks the pericardium, but may also implicate the endocardium, causing a rapid destruction of the valves of the heart and leading to septic infarcts in various internal organs. Another form of cardiac disease which was previously mentioned in the description of scarlatina gravissima and which we shall mention again in the description of scarlatinal nephritis, consists in an intense (toxic) damage of the *heart muscle*, the myocardium, showing itself by a dilated cardiac weakness, occasionally in the form of sudden cardiac death. From these affections also the rheumatic, or rather rheumatoid, form of scarlatinal endocarditis, which we must consider now is to be entirely separated. It develops occasionally in the same period with the rheumatoid joint affection, therefore, between the first and second weeks of the disease. Sometimes the signs of the affection are only noted after complete disappearance of the eruption, improvement of the scarlatinal affection and the return of subjective well being, during an apparent period of convalescence. Subjective symptoms are almost entirely absent and the complications cannot be discovered without auscultation; by this means, however, most markedly at or near the apex, but sometimes even most plainly at the base, a brief or longer soft murmur, synchronous with the ventricular contraction will be noted. A little later perhaps also a moderate distribution of cardiac dulness and a slight accentuation of the second pulmonary sound may be demonstrated. The patient who is still in bed does not complain and perhaps only a somewhat marked pallor of the face is conspicuous. Sometimes endocarditis is combined with pericarditis, and then with the corresponding objective phenomena decided symptoms appear.

It will be noted in not a few such cases that these signs disappear entirely, and in those cases in which there is an opportunity for prolonged continued observation the patients recover completely without signs relating to the heart. To a certain extent it always remains questionable whether there is an endocarditic process or whether only so-called accidental (functional) murmurs are present. But, on the other hand, from these rheumatoid, scarlatinal endocardites, unquestionably, valve lesions arise. Not infrequently is there an opportunity to note this, as the cases of cardiac murmurs, which are not very rare, that have positively developed during the course of scarlatina, are almost always found to disappear. I am, however, in possession of the facts of a case in which from a previously intact heart during an attack of scarlatinal rheumatism, the appearance of a murmur was observed and the gradual development of a typical mitral insufficiency could be followed step by step. Thus the scarlatinal infection in this direction is also treacherous, not being immediately dangerous to life but permanently damaging health. That in scarlatinal endocarditis the musculature of the heart (or the nerve-cells of the heart?) is not spared may be concluded from this, that during the existence of a cardiac murmur very frequently a more or less great irregularity of the pulse is observed. This is by no means so rare, even though there be no opportunity of demonstrating an endocardial complication occurring particularly in the stage of convalescence, often only in the sixth or seventh week and even later and then disappearing. This appears to occur particularly in those cases in which the affection is prolonged by nephritis.

The so-called *scarlatinal typhoid*, the relations of which to the disease are not yet quite clear, but which for the most part represents a benign and by no means frequent deviation from the normal course: A fever accompanied by moderate symptoms of depression and occasionally of marked disturbances on the part of the digestive organs and lasting for a long time without demonstrable local disturbances. Even this conception shows that not every febrile sequel of scarlatina that cannot be easily explained can be designated by the above name. And in every fever of this kind it is our first duty to search for the point at which resorption of material which may produce fever is possible. Such areas are numerous enough in the case of scarlatina. In my experience, especially the posterior pharyngeal wall and the posterior nares as well as the nasopharyngeal space should be considered. If there be seen—even although a previously present pharyngeal diphtheroid has disappeared—upon the posterior pharyngeal wall any decided muco-purulent secretion, a roughening, a superficial erosion or granulation of the mucous membrane, the possibility that the fever is due to this cause must not be overlooked and the result of a suitable local treatment often enough shows the correctness of this assumption.

The second point of origin of the septic post-scarlatinal fever is in the lymph glands. If these are found hard upon one or both sides and large and sensitive, the fever may be due to them even if they do not always suppurate. A third point of origin may be traced to one or the other region of the middle ear, which has already been mentioned above.

But, besides these septic post-scarlatinal fevers, there are individual cases in which even the most exact and careful investigation will not reveal the

source of the fever and in which the temperature curve does not at all show the intermittent or remittent character of resorption fever, but shows moreover a certain similarity to typhoid fever. As an example, the following temperature chart in which this fever occurred between the eleventh and twenty-third days of the disease, will be shown (Fig. 29).

A boy aged two and a half years was attacked, upon April 19th, with vomiting and fever, simultaneously with hoarseness and cough, in the midst of complete health; upon the second day of the disease, upon the arms and legs as well as upon the buttocks, there was at first a non-characteristic, later, a decided, eruption with marked redness of the pharyngeal areas. Upon the seventh day of the disease desquamation occurred, which continued into the fourth week, the scales consisting of large and long lamellæ of the epidermis, from the gluteal region as well as from the ribs. The cutaneous redness as well as the angina had disappeared in the second week, only at the angles of the mouth fissures formed with a lardaceous coating which required a long time for healing.

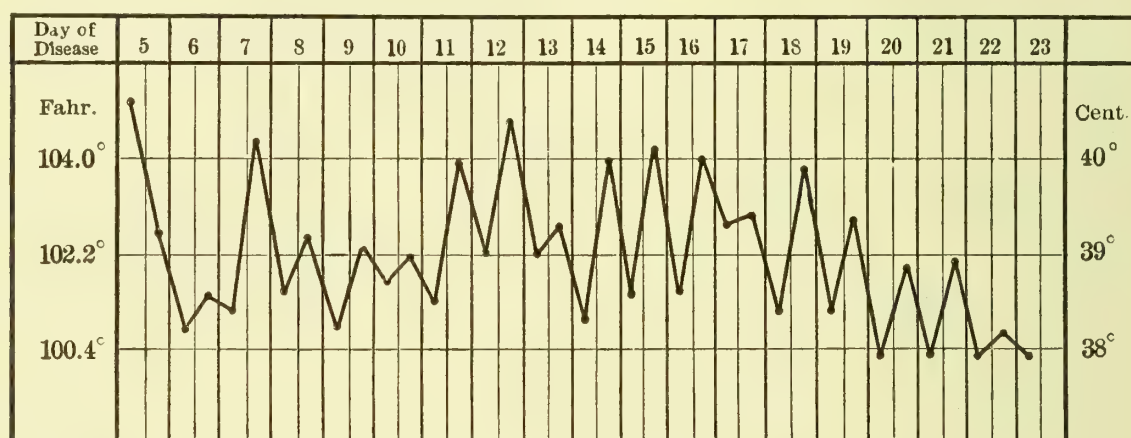


FIG. 29.

No lymphatic enlargement or otitis developed. The kidneys remained intact. For the continued fever from the tenth day on there was no explanation. A dry bronchitis occurred, which continued for a long time, the abdomen from the fourteenth day of the disease became tympanitic, was painful to pressure, and diarrhetic stools of a greenish-yellow color appeared. The spleen was not palpable. The child was irritable, now and then vomiting recurring, and with these symptoms the affection continued even longer than the time shown in the temperature curve. After the twenty-third day of the disease the temperature was no longer regularly taken; toward the middle of May recovery gradually occurred.

Apparently the process which produced the fever in this case developed in the digestive organs. It has been previously mentioned that under the influence of a scarlatinal affection, the mucous membrane not only of the nasopharyngeal space, but under some circumstances that of the entire intestinal tract shows hyperplastic swelling. It might be supposed that in such cases resembling a mild enteric course this deleterious influence of the scarlatinal poison affects the adenoid tissue which is so profusely present in the intestinal tract, as well as the mucous membrane, and thus leads to a condition of the digestive organs which resembles that brought about by the pathogenic agent of enteric fever. This cannot be determined with certainty as cases of this kind are not subject to anatomical investigation. In concrete cases, one point is still to be observed. Occasionally at the onset of enteric fever an eruption occurs which may closely resemble the exanthem of scarlatina. In

such genuine cases of enteric fever with pseudoscarlatina, the appearance of the rash (roseola), the proof of typhoid bacilli and agglutination are the points of support for the correct diagnosis.

A rare deviation of the regular course of the disease is shown by the *relapse*. By this we do not understand an increase of the redness upon the skin, which is frequently observed, causing the eruption to become plainer, which shows itself by a new rise in temperature, but the return of all of the symptoms of scarlatina, or at least of the eruption, after a complete cure of the primary affection.

This relapse which resembles the condition arising in enteric fever occurs in individual cases.

A boy aged seven, who suffered from a mild attack of scarlet fever from June 24th to July 8th, after he had been out of bed showed upon July 19th a decided swelling of the cervical lymph glands; following this, upon July 21st, with moderate fever, a new exanthem occurred, which in individual areas consisted of large macula and in others of small macula, having partly a measly appearance. Upon July 25th, the fever disappeared, swelling of the glands declined, and the eruption could no longer be noted.

In another instance a boy aged four was attacked upon June 30th with scarlatina, with quite an intense diphtheroid and lymphadenitis. During the period of desquamation, in which the angina improved, upon July 13th, with renewed but brief fever, a fresh eruption occurred upon the right forearm and right thigh.

In the course of a gland abscess during the existence of a nephritis I saw upon the fourteenth, and also upon the twenty-third, day of the disease a relapse and appearance of the exanthem with high fever. These relapses do not appear to be serious.

If the patient has resisted or escaped all of the described dangers which may occur in the course of the first two weeks of scarlatina, he has not yet escaped all of the dangers of one of the most treacherous infections; for, unexpectedly, after he appears to have been on the high road to recovery, often without any warning, an *affection of the kidneys* may attack him, which we meet with in many other affections, but in no other does it occur so frequently or so severely or take on such a substantive character as in the case of scarlatina. *Scarlatinal nephritis* may be looked upon as the prototype of infectious nephritis.

Scarlatinal Nephritis.—It is by no means a necessary consequence of the infection, as only a part of those affected, and at that a small part, shows this complication. In fifteen years in my private practice I observed 36 cases of scarlatinal nephritis in 358 cases of scarlatina, therefore, almost exactly 10 per cent. In 393 cases in the course of four years, in the Charité in Berlin, 77 cases showed a nephritis, that is about 20 per cent. (19.6 per cent.). This difference, however, is not so great as it appears, as in private practice there are many more mild cases than are met with in the hospitals. The epidemics of individual years vary greatly, climate and perhaps racial characteristics appear to play a certain etiological rôle. Johannessen reports of some Norwegian observer that he had 90 per cent. of renal affections in scarlet fever patients. But even in Norway the statistics of those physicians that have had a large experience do not rise above 20 per cent.

This is a remarkable difference from those complications which develop from the point of entrance of the supposed poison in the pharyngeal organs. Here in 60 per cent. of the hospital patients we found a diphtheroid mucous membrane inflammation.

What condition of the total disease brings about the renal inflammation is still unknown. Evidently it cannot be sought for in the severity of the infection at the onset, if we may judge from the intensity of the symptoms. For in quite a number of cases of nephritis, among them particularly the severest (for example, in my practice of 5 fatal cases, 4!), a mild, sometimes scarcely noticeable preliminary affection, with slight fever, fully developed eruption and mild angina precedes the complication.

It has already been mentioned above, that particularly the rudimentary cases often only become dangerous from the renal implication. And the period of the appearance of the renal affection in the course of scarlatina is against the view that it is an immediate action of the contagion. On the other hand, unquestionably, the development of scarlatinal nephritis from accidental external influences, possibly refrigeration, leaving bed too early, errors in diet and the like, may be rejected, for the development of nephritis cannot be prevented by the most careful nursing and diet and it affects those that are kept in bed constantly and patients that are only nourished with milk, to the same extent as those not so carefully treated. The influence of errors in régime are not to be entirely denied, but these must only be looked upon as auxiliary causes and do not by any means play the chief part, as, for example, in the development of pulmonary complications in measles. Especially the so-frequent appearance at a distinct period of the course stamps nephritis as an affection belonging to the scarlatina process. It is a late action of the infection. That it occurs at all is perhaps favored by a special sensitiveness of the organs or loss of resistance. The occurrence of such relationships of individual cell groups to certain poisons, particularly also to the group of parasite toxins, has been sufficiently determined with certainty by the new experimental etiology. Clinically, this view is favored by the circumstance that not so very rarely a distinct family predisposition to scarlatinal nephritis is met with in so far as often two or more children (I myself saw four) of the same family simultaneously show nephritis after scarlatina. It can scarcely be doubted that the kidney forms one of the excretory organs of the abnormal products, the symptoms appearing after the infection and in this manner the "haptophorous" cell groups of the organ may become diseased.

A fact which at first glance is peculiar has been mentioned several times, that this renal inflammation occurs during the period in which the rest of the process, the throat affection, the rash and the possible joint implication have disappeared. The first period of the symptoms which denote a renal affection appears at the end of the second or in the third week. Among my 36 cases, which for a great part I observed from the onset of the disease, the affection began seventeen times between the twelfth and fifteenth, ten times between the seventeenth and nineteenth days of the entire process. In the other cases the period was uncertain, or the onset of the affection occurred in a later period. Exceptionally, the renal disease may even occur several weeks

after an intervening period has preceded. Lately I noted this complication in the thirty-eighth day of the affection in a girl aged two years and nine months.

The child was taken ill on January 1st, and upon January 5th was sent to the Charité. The course of the disease was not particularly severe, being combined with a mild diphtheroid. The urine, constantly examined, was still free from albumin upon February 4th. Upon February 7th, a mild hemorrhagic nephritis occurred, which began to disappear upon March 3d.

This paradoxical condition, which is analogous to certain symptoms of late diphtheria, as well as to some infectious diseases of very long incubation, was explained by some physicians in that they assumed that the renal affection existed from the onset of the disease and only produced symptoms late in the course of the malady. It is true that with high fever, in the first week albuminuria and casts occur in the urine; but after defervescence this disappears completely. In dozens of cases which were carefully examined for this sign, various authors, especially Thomas, found that the composition of the urine for days and weeks after the primary febrile albuminuria was again completely normal before scarlatinal nephritis quite suddenly appeared. From my own experience, I may throughout confirm the views of Thomas. According to my investigations, as well as those of other authors, for example Sørensen, the anatomical changes in the kidneys of scarlet fever patients that perish in the first week are entirely absent or but very insignificant. It is not easy to comprehend how especially the last named author refers the development of nephritis to the first period of the entire process. This view nowadays is shared by but very few physicians.

In a pathologico-anatomical, as well as in a clinical respect, scarlatinal nephritis shows a character which naturally is also peculiar to other infectious renal inflammations, but which is particularly prominent in scarlatina, and at least in the recent cases and in those that are at all well developed it is never absent: This is the hemorrhagic character of the pathological process. In the anatomical examination this is well defined to the careful observer, even if not always macroscopically still microscopically, naturally, provided that the organ is not hardened in alcohol, which destroys the hemoglobin. Sørensen found in 15 carefully examined cases of scarlatinal nephritis numerous, mostly hemorrhagic casts in the uriniferous tubules, and in 11 cases several times, "yellowish masses" in the capsular space. Kaufmann describes acute hemorrhagic change in the kidney due to scarlatina. I have examined various cases of scarlatina carefully and agree with those observers that have found at the onset of the disease, especially in the grave cases that succumb early, a marked hyperemia of the organ but as yet no signs of inflammatory changes. Only during the period in which the children succumb to the consequences of nephritis (cardiac asthenia and dropsy, especially pulmonary edema or uremia) does the kidney show distinct signs of hemorrhagic inflammation, above all, in the glomeruli. The accompanying figure (technically a not very complete reproduction of a photogram) gives an example of such a hemorrhagic glomerulitis.

The thick opaque capillary loops, rich in nuclei are seen, from which

intense hemorrhage (*b*) has occurred. These fill a part of the capsular space, the epithelium of which has proliferated. The convoluted uriniferous tubules near the glomeruli from which hemorrhage has occurred are filled with the exuded blood (*cc*). But we are not dealing here with a simple collection of red (and corresponding white) blood corpuscles in the lumen of the canal, but its entire contents, usually including the epithelium, have been moulded together in a coagulated mass, in which no longer any nuclei of the epithelia are discernible but only a homogeneous or slightly granular mass is noted, in which red blood corpuscles, usually of a small diameter, may be seen. Here, therefore, the blood which has exuded from the glomeruli as it appeared, produced a toxic action of the epithelia. In such areas, by means of methods

which allow the fact to appear, always larger or smaller globules of fat partly still in the form of epithelium may be noted. In the loops of the uriniferous tubules I have never seen such hemorrhagic coaguli. Hemorrhages, however—in so far as we are justified in concluding from position and form of the epithelium—occur also in the spaces between the renal tubules; here, however, they are not combined with such epithelial necroses but simply lie in the lumen, which could occur in no other manner but by diapedesis. In the collective tubules, finally,



FIG. 30.

clogging by hyaline casts is found and here also without deeper implication of the epithelium, the nucleus of which is still retained. Only here and there a desquamation of the entire epithelial cylinder from the basic membrane of the tubule is shown. The massive clogging of the straight canals (here and there also of the loop canals) has a further consequence: that of urinary stasis in the entire area of the affected collective tubules. Thus the convoluted canals of the labyrinth which are not affected in the previously described manner are found *dilated* to a great extent, their lumen large, their epithelium (otherwise unaltered) pressed against the wall. This is also true of the intercalary portion as well as of the convoluted tubules. The damage to the active part of the kidney consists, therefore, in a disturbance of the normal function of the glomeruli (especially in the excretion of water) secondly in a destruction of a part of the secreting epithelium of the labyrinthian part of the canals, and thirdly in stasis of the secretion in the remaining part. This is the process in the pure, severe cases (for example in a case dying after nine days of anuria).

In the milder cases, the two deleterious effects upon the parenchyma of the kidney are of but slight extent, whereas the hemorrhages from the glomeruli may even be considerable. In the formation of casts in the uriniferous tubules, it will depend particularly upon their density and adherence as to whether the consequences will be severe or mild.

From the observation of these findings (fresh frozen sections of kidney hardened in formalin) it will be seen that in this form of nephritis the *primary* damage occurs in the *vascular* arborization, therefore, in the interstitial part of the glandular organ (this, for example, is not so marked in the diphtheritic kidney). Most noticeable in the glomeruli, and first studied by Klebs and afterward by numerous other investigators, this pathological change has led to the designation of the scarlatinal kidney as a glomerular nephritis. But this does not mean that only the glomeruli are implicated. Although I cannot recognize the periarteritis described by Fischl in the small arteries, the circumstance that the capillary net which surrounds the labyrinthian tubules allows blood to exude proves that even there the endothelial covering of the capillary tube is diseased. This may be more marked in the secretive portions of the capillary system than in the nutritive area.

That in consequence of the damage to the capillary wall, not only the previously described hemorrhages but also in more or less numerous areas, collections of leukocytes appear around the vessels, is readily comprehended. In the *recent* cases of pure scarlatinal nephritis, this finding plays no great rôle. Particularly dense is this noted in areas in the boundary layer in the vicinity of the curved arterial twigs, around the glomeruli and upon the surface of the kidney.

If the scarlatinal nephritis has lasted for weeks or months previous to the anatomical examination, the interstitial conglomerations of cells may reach high grades and may lead to an extended change in the parenchyma, necrotic areas, connective tissue proliferation and contraction, producing an entirely different picture. But even in these cases the interstitial inflammation will be prominent. *Septic renal disease* which occurs in connection with severe diphtheroid, in a restricted sense differs in its anatomical appearance from the scarlatinal, more closely resembling other septic processes.

In fatal cases in which scarlatinal nephritis enters upon a chronic condition, it usually takes the course of a very slow contracted kidney, which requires at least a few years for its development.

The comparatively slight mortality from scarlatinal nephritis, in spite of the frequent threatening symptoms, denotes in the main that the damage to the kidney is not too severe. Of 36 cases observed by me, 5 died, a mortality of 14 per cent. In the hospital, during the years 1894 to 1898 the mortality from renal inflammation amounted to 26 per cent.

Clinically, the appearance of nephritis in the scarlatinal picture in quite a number of cases is not characterized by subjective symptoms. The parents notice a disturbance of convalescence in their child, either by a swelling of its face or by the odor or composition of the urine. More than once have I been called by a mother to see her child, with the remark that its urine resembled hers during the menstrual period. Otherwise the child was quite

well. With these symptoms the inflammation of the kidney not rarely runs its course from beginning to end.

In other cases the disease begins with new general symptoms. The temperature rises, either in the form of a single daily rise to a moderate or even to a decided height (over 104° F. even to 105.5° F.), with chills, burning or sweating, or the fever continues for several days, even lasting for weeks, showing a remittent course. The cause of these variations in the reaction is not known. The intensity of the nephritis and of the fever do not always run parallel.

Then vomiting is often frequent, which may be repeated many times during the first days, to this there is added headache and restless sleep; anorexia is also present.

The pulse often rises with the fever, but, on the other hand, abnormal slowing and arrhythmia are observed. Thus in a boy aged seven years, upon the sixth day of a febrile nephritis (terminating in recovery), I counted 64 regular beats per minute, in another case, in a boy aged eleven years, a nephritis began upon the nineteenth day of the scarlatina, the pulse was from 96 to 100 per minute; in the second week of the renal inflammation it fell to 60 to 66, rising again as recovery advanced.

Slight swelling due to dropsy of the subcutaneous cellular tissue can always be observed upon careful examination; above all, a slight edema of the face and a brief pitting upon pressure with the finger upon the tibial surface and upon the sternum. Often dropsy is much more marked, especially in the legs and upon the buttocks, being combined with a watery transudation in the abdominal cavity, in the pleura and in the pericardium.

If the urine has not been examined previously the symptoms just mentioned lead the physician to an examination and now the great change that has occurred is discovered. In place of a light yellow or light orange colored, clear, profuse urine, its characteristics a few days previously, a turbid reddish-brown or dark red, opaque fluid is noted, which shortly after standing deposits a more or less dark cloudy sediment. If the daily quantity is measured it is found to be decreased, for example, from the previous 1,000 to 1,200 cc. its volume may be decreased to 600, 500 or even less. In keeping with this, the specific gravity is raised. An examination of the filtered fluid shows more or less marked contents of albumin (2, 3, up to 7 per thousand and more) and the dark color is shown to be due to an admixture of blood, the coloring matter being determined by the guaiac test or by Heller's sediment test. If the admixture of blood is not very marked, the urine is light red in color, sometimes resembling the washings from beef. If held to the light it is shown to have a greenish tinge.

An examination of the sediment shows numerous erythrocytes; they are often conspicuously small and not, infrequently, besides a small undamaged erythrocyte, or an erythrocyte appearing as if it had been dissolved, a brown granular detritus may be noted even in freshly voided urine. From this it must be concluded that not rarely also in the kidney perhaps even in the renal vessels a decomposition of the red blood cells has occurred. I noted once during the period in which nephritis usually occurs a severe hemoglobinuria with a rapidly following fatal termination.

Besides blood corpuscles, there are found in the sediment various hyaline casts of varying character, large and small, long and short, smooth and uneven; often red blood corpuscles are found enclosed in the casts or are adherent to them. Some casts are purely epithelial; some are impregnated by urate salts, others carry finer or coarser globules of fat, again others contain leukocytes. Finally, waxy casts are also seen. In recent cases, leukocytes are not very predominant, renal epithelium is not scant. Cells with fat granules are quite rare; I once saw them on the first day of a nephritis in a boy aged seven years; the course of the affection was mild.

Besides these changes, which are due to the anatomical disturbance in the kidney, in the course of the last few years it has been attempted to determine the diminution in functional activity somewhat more accurately, in that the effort has been made to determine the change of the molecular concentration by means of physical examination. The results obtained by *cryoscopy* of the urine up till now are, however, by no means conclusive. The function which can be determined by simple measurement, for the present, is the only practical one from which we may form an opinion, both in a diagnostic as well as in a prognostic respect: *the excretion of water*. The lower this falls the more serious the prognosis. The daily amount of urine, not the albumin contents, and certainly not the composition of the sediment, inform us regarding threatening danger.

In the mild cases the excretion of urine does not fall below 400 to 600 cc. per day. For a week or two the previously described composition of the urine remains the same, the daily quantities become larger, the color lighter, and the daily quantity of albumin smaller. Finally, the albumin disappears entirely. But the sediment does not disappear at once; even days after no trace of albumin can be proven by the most delicate tests, the desquamation of epithelium and casts still continues. The total duration of the affection is about three weeks. The subjective difficulties are always moderate; a certain lassitude is even shown by the patient that remains in bed and he always shows an unusual pallor and swelling of the face, even in the cases in which no marked dropsy is present. In fact dropsy may be absent entirely in the mildest cases. Gradually as recovery occurs the normal healthy color of the face returns.

This is different, however, in severe cases. The subjective difficulties are greater and very often the patient complains of pains in the renal region which are increased by pressure; these pains otherwise are generally localized to the abdomen. I have never seen severe attacks of colic due to acute inflammatory changes in the kidney as have been described by Israel.¹ The appetite is gone and diarrhea is often present. The pallor is of a high grade, the face occasionally appearing waxy pale, almost transparent.

The diminution in the amount of urine is conspicuous; in a few days the excreted amount falls to 150, 100, 50 or even 0 cc. and this anuria may last for days (in a case recently observed nine full days passed before death occurred). However, in the urine that is excreted there is sometimes observed the paradoxical phenomenon that it contains less of a pathological

¹ Deutsche med. Wochenschrift, 1902, Nr. 9.

admixture regarding albumin as well as sediment than the previous profuse urine. This can hardly be explained in any other manner than that such a secretion occurs from areas of the kidney that are but slightly attacked, the convoluted tubules of which are not clogged. The anatomical investigation in the severest cases also shows by no means a simultaneous severe affection in all areas of the glandular organ.

Now, as a rule, but a few days pass before the symptoms of *uremia* appear. Headache and vomiting recur, the child becomes restless, anxious, tosses itself about from side to side, crying and moaning; the tongue shows a smeary thick coating, the breath has an ammoniacal odor and in the expired air ammonia can be demonstrated; appetite has disappeared completely. Frequent desire to micturate and fecal evacuations occur, but not a drop of urine can be pressed out. Gradually this condition of excitement is succeeded by somnolence, the child is quite apathetic, with closed eyes; it snores and if awakened, rapidly returns to a state of sopor as if under the influence of alcohol, or it is even entirely unconscious, and now the picture that has become monotonous is varied by the sudden appearance of general spasmodic attacks resembling epilepsy. Sometimes this condition is preceded by partial, even quite monoplegic spasms, for example, in one half of the arm or one half of the face, and then only does the major attack, with general tonic-clonic spasms, pupillary rigidity, foaming at the mouth and complete unconsciousness take place. These attacks may succeed one another until a rapid fatal exhaustion occurs. All the spasms cease after a number of attacks and consciousness returns. Then those about the child are appalled by a new phenomenon, the child has lost its sight. The appreciation of light and darkness may have ceased entirely. This uremic amaurosis is not due to any change of the eye-ground but it is to be looked upon as a toxic disturbance of function in the light centre of the cerebrum. This is favored by the rapid disappearance of this pathologic symptom as well as by the observation that the amaurosis before it disappears entirely, sometimes changes into hemianopsia.

This convulsive catastrophe sometimes has the appearance of an actual crisis. Soon after the disappearance of the severe spasms the quiescent urinary secretion returns, a highly intense bloody urine is voided in rapidly increasing amounts, the blood contents then disappear simultaneously, the other threatening symptoms abate and the patient recovers. In some few cases there is added to this acute attack a prolonged permanent condition of psychical disturbance, a melancholic depression with renewed spasmodic attacks. This, however, occurs almost always only in individuals with a nervous taint.

Unfortunately, often enough, even during the attack, death occurs.

The material or the materials which produce this influence of a true intoxication upon the cerebrum, giving rise to this symptom-complex, in spite of numerous investigations, have not yet been determined with certainty. That this intoxication is due to a retention of products which have not been excreted can scarcely be doubted. It may, however, be remarked here, that the severity of the uremia in all cases is not parallel to the degree of anuria. I saw a fatal case of uremia (in severe scarlatinal nephritis), in which the spasms, that in a few hours caused death, occurred upon the after-

noon of a day in which the secretion of urine amounted to 600 cc. Two days previously, however, the uremic headache had already appeared. Just this, in my opinion, is in favor of the fact that scarlatinal uremia is not alone due to action of the retention of a product of excretion known to us, but to the formation of new toxic products, the retention of which in a number of regions of the kidney is sufficient to give rise to severe even fatal damage to the nervous substance.

Strauss,¹ in his examinations of the blood of uremia in chronic renal cases, appears to have come to a similar conclusion when he says that "the increase of the molecular concentration of the blood is an accompanying symptom, *not the cause* of uremia, that the poison which produces uremia is mostly found in those persons in whom also other pathologic substances are found in the blood in abnormal profuse amounts." But, naturally, uremia is usually to be the more feared, the more marked and continued the diminution of the excretion of water, because in this case the substances which are soluble in water remain in the kidneys.

This condition, parallel with the excretion of water, is shown by a second symptom which is a regular accompaniment of severe scarlatinal renal inflammation: *dropsy*.

Although it is not entirely absent in mild cases, this symptom only becomes intense when combined with a low excretion of urine. The face, legs and arms swell, the abdominal covering becomes markedly edematous, as well as the scrotum and penis. At first the swelling is firm, so that the pressure of the finger soon disappears, but after a prolonged existence it becomes flaccid and soft as in other cases of anasarca. To this must be added the transudate into other parts of the body, ascites, hydrothorax, hydropericardium, and in some cases very serious pulmonary edema and edema of the glottis. Regarding the development of dropsy, much debate has arisen. It was believed that simple retention of water was not sufficient to explain anasarca, there must be added especially an alteration of the vascular walls. In fact, I recently noted in the skin of a dropsical child inflammatory changes about the cutaneous vessels similar to those noted in recent cases of scarlatina. But whether this is necessary, is very questionable. The water that the organism does not succeed in excreting must remain somewhere, as the lungs are not able to dispose of it; but, while it cannot be denied that dropsy may occur with a plentiful secretion of urine, being absent upon a diminution lasting for any time, the latter condition refers to a very few days, and in the former circumstance another point must be considered, to which various authors have already called attention (for example Fürbringer), the importance of which must not be undervalued.

Scarlatinal nephritis also has an effect *upon the heart*. There are not many diseases which, like scarlatinal nephritis, even after a brief existence, are capable of bringing about a decided dilatation (and under some circumstances also hypertrophy of both ventricles). This action upon the heart muscle not only can be proven at the autopsy, but shows itself by a dissemi-

¹ Die chronischen Nierenentzündungen in ihrer Einwirkung auf die Blutflüssigkeit. Berlin, Hirschwald, 1902.

nation of cardiac dulness, by the diffusion of the apex beat and the influence upon the pulse (at the onset often abnormal slowing, see above, later the pulse wave becoming small and low upon increased cardiac action), but also by very conspicuous clinical signs denoting a diminished function of the heart. Then there develops, often only after a successful recovery from a uremic catastrophe, a new series of difficulties of another kind. The child again becomes restless, cannot sleep, loses its appetite, begins to complain, this time, however, not regarding headache and nausea but of a tightness and pressure in the chest, of dyspnea and cardiac anxiety. Now the child becomes dyspneic without any cause of this symptom being discernible on the part of the lungs. The condition is one of cardiac dyspnea. About this time, as a rule, dropsy and, later, transudation into the serous cavities begins to conspicuously increase. The secretion of urine, however, does not diminish markedly and the sediment shows a great tendency to the formation of urates. This new increase in dropsy is apparently not only in connection with the disturbance of the renal function but for a large part it is due to cardiac weakness. Thus we meet here for the second time (or including endocarditis, the third) with a danger which threatens the heart, due to scarlatina.

These infrequent cases, in which scarlatinal nephritis leads to a marantic condition, in which, with a general high-graded dropsy, enormous swelling, especially of the scrotum, deathly pallor, complete anorexia, sometimes accompanied by profuse diarrhea, cool and cyanotic extremities, scarcely perceptible pulse, producing a pitiful condition which often drags along for many weeks and then, on account of many varieties of complications, bedsores, phlegmons, gangrenous erysipelas, pulmonary hypostasis, brings about the fatal termination—finds its explanation particularly in the severe damage to the cardiac power. Naturally, the phenomena of chronic uremia may increase the difficulties. But even during the first weeks of a renal inflammation the symptoms of decided cardiac asthenia may be intermingled with those of uremia. Such cases, in my opinion, always show a very serious prognosis. An important sign of this combination is *the increase in size and tension of the abdomen* which may be determined in some anuric patients. This is due to a high-graded enlargement of the liver in consequence of stasis, and this again is a consequence of the failure in the circulation of the blood.

The cause of the fatal termination of anuria is not always the nervous system. A child that was recently observed by me, in which anuria existed nine days, sat in its bed, played with its toys, was restless from time to time, but in most respects did not present a condition that would cause an inexperienced person to suspect the terrible danger which existed for the little patient. Not a spasm occurred before death, and the mind was clear. Finally, in the course of a few hours the symptoms of slight stenotic respiration appeared (consequent upon edema of the glottis) and then the child rapidly succumbed in a severe collapse. In this instance apparently not the usual uremic cerebral intoxication, but a cardiac intoxication was the decisive cause.

Finally, the same condition must be assumed, in which the fatal termination of severe nephritis is brought about by *pulmonary edema*; on the other hand, the addition of a pulmonary affection is to be looked upon as a dangerous secondary mixed infection.

In a case of this kind observed by me, in a boy aged one year and a half, the renal inflammation occurred on the thirteenth day of a medium severe scarlatina; upon the fourth day after this the secretion of urine fell to 50 cc. per day and at the end of the second it again rose from 50 to 100 cc. without uremic symptoms appearing. In the beginning of the third week, in the decidedly dropsical child, a high irregular fever and a pulmonary inflammation occurred, during which the edema almost completely disappeared. At the end of the third week of the nephritis death occurred, being ushered in by tracheal râles. The autopsy showed enlarged kidneys, the parenchyma of a yellowish-red consistence; hypertrophy of the left ventricle; lobar pneumonia of the right lower lobe.

If all the dangers are considered which threaten the life of a case of scarlatina complicated by renal disease, we are actually astonished that the prognosis in scarlatinal nephritis in general is not so serious as might be supposed from the first view of the case, that, moreover, upon the average six-sevenths, in many epidemics still more patients, recover from this condition.

It is true, whether acute nephritis is mild or severe in its onset, in the background there still hovers for the apparently convalescent patient a threatening spectre: the transition of the acute into a subacute and chronic affection.

Formerly this eventuality was scarcely considered, denied by some physicians, or at least looked upon as very exceptional. Since convalescents are constantly examined and for weeks kept under observation, and the renal secretion investigated, we have become convinced that this development is by no means so rare, even though the children subjectively and—apart from the composition of the urine—objectively, scarcely show disturbances in their general health. Often enough, however, in the further course of the affection a decided rekindling of the disease interrupts this condition, which then takes a similar course, giving rise to dangers like those of the first onset of the affection.

Usually the transition into this permanent condition occurs in the manner that after the complete disappearance of the dropsy, and of the possible uremic symptoms, and after the reappearance of a profuse urinary secretion, the chemical examination of the urine shows a permanent excretion, often of scant, frequently also of profuse, amounts of albumin. This excretion of albumin may often show a distinct *orthotic* character, i. e., it disappears when the patient is in the recumbent posture and reappears as soon as he assumes the erect posture. Later it may, however, lose this character. The color, weight and amount of the urine often show no decided deviations, at most that urine following a period of diminished excretion, this being sometimes succeeded by decided polyuria; but the microscopic examination of the sediment teaches that we are still dealing with a mild hemorrhagic form of nephritis. Besides casts of various kinds, granular, hyaline, waxy, also some containing blood corpuscles, almost without exception some few red blood cells are met with; however, as a rule, many more leukocytes are present; finally, almost constantly either few or a large number of fatty granular cells are found, sometimes free, sometimes adhering to casts. Not infrequently *intermittent albuminuria* may be noted.

This continues for weeks. The weeks become months, the months become years; and if albumin were not present in the urine, the children, who usually

only have a pale color and complain more or less of headache, would hardly be considered ill. But the question always arises: What becomes of them? This is certain: In favorable cases, even after an existence for years, the albuminuria may disappear completely; this usually occurs in the period of puberty. A case of this kind occurred in the son of a physician and was determined by the father. Secondly, from a nephritis of this sort, within a few years or after a decade, a complete typical contracted kidney may arise. An instance of the first kind I have observed myself, and of the second Dixon Mann gives a very striking example.¹ It can scarcely be doubted that not all the cases which continue unimproved in youth finally take the course observed by Mann. Thus, we meet here with another danger of scarlatinal infection which casts a shadow over the entire future life of the patient who is fortunate enough to recover from scarlatina. For although such patients during the entire life may show a certain degree of health they hardly ever reach old age.

[Such persons show a remarkable tendency to develop albuminuria (sub-acute or acute nephritis) upon exposure to dampness, especially dampness associated with cold, or upon the occurrence of any acute disease. I have for some years been in the habit of interrogating patients suffering from renal disease, in regard to scarlet fever, and in particular post-scarlatinal dropsy in their childhood, and have been astonished at the frequency of the association of these conditions in individuals who have for many intervening years enjoyed excellent health. A much larger proportion of those who develop nephritis in adult life give a history of severe scarlatina with or without dropsy in childhood than a history of the milder forms.—ED.]

There are still some complications, which, although not belonging immediately to the clinical picture of scarlatina, must be considered as they sometimes influence the entire course of the affection.

Little has been said regarding an *implication of the respiratory organs* in the affection. The diphtheroid mucous membrane affection of these, even in severe cases, does not pass beyond the larynx. The ominous importance of hoarseness and the stenosis which appear have already been noted. But occasionally there is added an intense purulent inflammation of the bronchi and lungs which may reach such a degree of severity that this alone is sufficient to cause the unfavorable termination.

Recently, in the clinic, I saw a boy aged five years who showed high fever, while the eruption was still at its acme. He succumbed upon the sixth day of the disease, showing severe changes in the bronchi and lungs. The palate was hardly red, there was only medullary swelling of the lymphatic tissues, neither the tonsils nor the larynx being implicated; however, the lower lobes of the lungs upon both sides were of tough consistence and of a dirty brownish-red color. Upon section, a bloody edema was noted, but air was also present and from all bronchial openings fluid pus escaped. Upon both pleura fresh fibrinous deposits. The heart was very relaxed.

¹ Heubner, Chronische Nephritis und Albuminurie im Kindesalter. Hirschwald, Berlin, 1897, pp. 54 u. 52.

In a second case, in a boy of ten, who died on the fifth day of the disease, there was found in the left lower lobe, a disseminated purulent capillary bronchitis, lobular infiltration and edema.

I once saw in a nursling of six months, upon the sixth day of scarlatina, the appearance of a severe capillary bronchitis, from which, however, the child recovered.

The bacteriological examination of the bronchial mucus of the cases occurring in the clinic, in which bronchitis was present, showed the presence of streptococci, so that we will not be far wrong if at least in the severe forms of bronchopneumonia we regard these cases as due to the aspiration of these microbes which play such an important rôle in the secondary infections in scarlet fever.

The *organs of digestion* are with comparative rarity affected to any marked extent. Sometimes jaundice is noted in scarlet fever; it may be of a catarrhal nature and does not influence the course of the disease in a prominent manner. I have seen it occur also in septic cases in which, however, it presents an ominous sign.

Severe diarrhea is sometimes met with in septic pharyngeal affections; it only occurs in the severe and usually fatal cases, taking place in the last few days before death, and is due to an inflammatory swelling of the mucous membrane, especially of the large intestine. Here perhaps streptococci are also the cause.

The *central nervous system* in the case of scarlatina, similar to the other acute exanthemata, occasionally presents severe disturbances, which are so closely connected with the infectious disease that it is difficult to speak of them as mere accidental occurrences. A case recently observed by me is an example of this:

A girl aged eight years was attacked upon November 22, 1900, by diphtheria, which was cured by antitoxin treatment. Upon December 2d a new illness appeared which at first was supposed to be a serum exanthem, but soon showed itself to be scarlatina complicated by severe diphtheroid. Great destruction in the pharynx, numerous lymph gland abscesses and nephritis prolonged the disease for over two months. Up to the middle of February, 1901, fever was present; thence on there was steady improvement, with a good condition and a fair appetite. But still a frequent pulse was present; nothing abnormal could be noted in the heart.

Suddenly upon February 19th, early in the morning, with a clear mind, clonic spasms occurred in the left half of the body, followed by slight left-sided hemiparesis and some mental confusion. Upon the afternoon the spasms recurred but were limited to the left extensor digitorum pedis. Upon April 6th, the child was brought to my office, spasms had not recurred, no paralysis, heart normal, but upon April 7th, again left-sided spasms occurred in the arm and leg, which increased from time to time in severity so that in the second half of May they occurred daily. From then until October the spasms did not cease, occurring almost daily, and only by an energetic bromide treatment were they somewhat suppressed. Other disturbances of the cranial function were absolutely absent. Intelligence was retained. Also the power of movement in the left half of the body was but very slightly influenced. Since that time I have not seen the child.

It can scarcely be doubted that here a superficial meningo-encephalitic focus had developed over the right central convolution during the attack of scarlatina. The spasms had the entire character of those occurring in Jacksonian cortical epilepsy.

Combinations of scarlatina with other specific infectious diseases occur with great variations.

Especially important is that occurring with *bacillary genuine diphtheria*. Quite often not only in the same locality do scarlatina and diphtheria occur endemically—which has led to the erroneous assumption of a close relationship of both diseases and especially of scarlatinal diphtheroid with true diphtheria—but even in one and the same family scarlatina and true diphtheria may occur side by side. I have noted instances of this in which children suffered from unquestioned scarlatina without diphtheria, whereas the father simultaneously suffered from bacillary diphtheria which was followed by severe, prolonged paralyses.

If both affections combine in the same organism, it is much less serious if diphtheria is added to scarlatina than inversely. Each year, in the clinic, one or the other case is observed in which genuine Löffler bacilli can be determined in the pharyngeal parts, these areas then for the most part being covered by dense membranes. If the specific treatment is begun at once, the second infection does not materially add to the difficulties of the first, even if the scarlatina should be of a serious character. This I saw in a severe scarlatinal diphtheroid, in which later on, not only new deposits in the pharynx but also the walls of a deep and distributed ulcer cavity in some lymph glands in the neck covered with membranous deposits occurred. Everywhere the typical Löffler bacillus could be demonstrated. After specific treatment, which was employed at once, the diphtheria rapidly disappeared and finally the very ill child recovered completely. Naturally, when the true character of the pharyngeal affection is not recognized, that laryngeal stenosis, descending croup or true diphtheritic paralyses may follow a “scarlatinal diphtheria” is easy to understand, but does not alter the fact that the usual diphtheroid pharyngeal infection has nothing in common with true diphtheria.

The condition is much more serious if a scarlatinal infection is secondarily added to diphtheria. Then it avails but little that the primary affection has been successfully and specifically treated. In the winter of 1894–95, while the curative serum treatment was in full swing in the diphtheria division of my clinic, a scarlet fever epidemic of 12 cases occurred, almost all arising in November and December. The original diphtheria patients for the most part were medium severe cases and were at once treated with curative serum; in spite of this, 3 of the 12 cases died, therefore 25 per cent. The originally diseased diphtheritic parts, after the appearance of scarlet fever, were attacked by a hemorrhagic necrotic inflammation. The transition of the membranous diphtheria to a necrotic and ulcer-forming diphtheroid inflammation could be well followed. The cause of death is always due to sepsis, in one case with the addition of jaundice, in another of the hemorrhagic diathesis.

The combination of *varicella* and scarlatina, especially if the former is added to the latter, runs its course without disturbance. Not rarely is scarlatina added to varicella in the manner that the erythema, as from a wound, takes its point of origin from a scratched varicella pustule. Then the scarlatina does not always run a favorable course but develops a stubborn nephritis or other complications.

Once, in a girl aged nine years, I saw scarlatina develop in connection with varicella. To the scarlatina there was added a severe erythema exsudativum multiforme, to this simultaneously there was also added hemorrhagic nephritis and a severe hemorrhagic diathesis resembling scurvy, with marked hemorrhages from the gums and, finally, measles appeared. But from all these diseases, after an illness of three months, the child finally recovered completely.

Occasionally in convalescence from scarlatina, the appearance of purpura is noted. Two cases which occurred a year or two ago in my clinic, after a few weeks, terminated in complete recovery.

Regarding the complication of measles and scarlatina this has been described under measles (which see under Measles).

Puerperal scarlatina, according to the investigations of Sörenson, as well as of other authors, is nothing else but the usual scarlatinal infection which finds entrance by way of the damaged parts. The previously mentioned author found the diphtheroid infection in the peritoneum and in other wounds of the genitalia instead of in the pharyngeal organs.

In a pregnant woman aged thirty-five (toward the end of pregnancy), upon the third day of the disease, I saw the birth of a dead child; there were no signs of the eruption present. A woman aged thirty-four years who was nursing her child during a medium severe attack of scarlatina kept on nursing without the child being attacked.

DIAGNOSIS

In well developed cases the scarlatinal rash has a characteristic appearance. The fine, delicate, closely situated elevations seen at the onset of the disease, which, after the general cutaneous exanthem has appeared, remain during the entire course, are not met with in the same manner in other eruptions of a similar nature. At most, the "triangular form" of the prodromal variolous eruption might be assumed which sometimes exactly resembles the scarlatinal exanthem, even including the deep fine elevations, but this is so limited to a triangular space upon the thigh or the shoulder that the differentiation may be very readily made.

But there are acute diseases in the early period of which a *scarlatinoid exanthem*, an eruption, appears simulating a form which is not rare in scarlatina and which may then give rise to grave errors. This is noted in enteric fever and in acute lobar pneumonia in children as well as in adults. General cutaneous erythema even with succeeding mild desquamation particularly occurs in the first days before the previously mentioned characteristic symptoms of the disease have developed. I know of a case in a lady whose severe enteric fever which terminated fatally was incorrectly looked upon as scarla-

tina by a prominent diagnostician. In children I have much more frequently known the mistaken diagnosis of pneumonia to be made. It will always be well to remember the small prominent points in the exanthem before a diagnosis of scarlatina is made.

Besides there are also toxic exanthems which may give cause for confusion to less experienced physicians; thus, we occasionally see drug eruptions of a scarlet red color produced by quinin and antipyrin, but the injection of the deeper layers which is so characteristic of scarlatina (upon pressure with the finger), the *raie blanche*, and the unevenness of the skin are absent. For a long time the similarity of the rash of atropin to that of scarlatina has been known, which even once led to regarding belladonna as a preventive against scarlatina. Further, the toxic products contained in the serum of animals often lead to a scarlatinoid eruption. These forms of serum exanthem, especially in the diphtheria departments of hospitals, often are the cause of great anxiety. They may appear with severe fever, with headache and vomiting, and not infrequently are the palatine parts inflamed, even new deposits occurring. Briefly, the entire picture of beginning scarlatina is present. There are cases in which the question whether we are dealing with scarlatina or not, must remain undecided—even the combined opinion of such experienced eyes as those of a Widerhofer and of a Kaposi have been impossible to decide this question at a first glance.

In these cases another property of the scarlatinal rash which makes the diagnosis difficult must be considered: that it by no means always reaches the full development which was previously described as so characteristic. On the contrary, in unquestioned cases it quite frequently remains in a stage of pale, indistinct, rose-colored maculæ, in which confluence does not occur, without attaining a scarlet color during its entire course. Sometimes even distinct spots do not appear but we only find a slightly developed erythema upon the trunk and upon individual parts of the extremities. Exanthems of this kind naturally occur in quite a number of other affections. Apart from the eruption due to serum, we find this in a well developed manner in the scarlatinal form of rōtheln. But it will be opposed that this disease runs its course without fever! That would be a decided point of difference if there were not cases of scarlatina without fever, or at least with only a slight initial rise, which may have disappeared at the time of observation. A short time ago, when in consultation with one of the first physicians of Berlin, I had to give an opinion in a case in which he was in favor of scarlatina, while I was in favor of rōtheln, without either of us being able to give decisive proofs for his opinion. The further course of the disease favored my opinion in so far as no nephritis or other serious difficulty arose. In these difficulties it becomes quite clear how much the clinician owes to the bacteriologist, in all those cases in which an unquestioned etiological diagnosis is possible. At the bedside, in doubtful cases, it would be well to examine the entire surface of the body; frequently, at least here and there, an area is noted in which the fine papular character of the rash shows the nature of the disease. Also the conditions of the oral and pharyngeal cavities which will be described later may aid in this.

An influenza, also with cutaneous erythema, occurs, which may resemble

a feebly developed scarlatinal eruption. A few years ago, in the family of a colleague, I was required to give an opinion in which, simultaneously, fever, and an angina with a beginning exanthem were present; the rash having the character of a fleeting form of scarlatinal erythema. Only the circumstance that almost within five days all the cases occurred suddenly, all the patients being adults, and in a short time recovering without complications favored influenza against scarlatina. As no expectoration was present no decision could be given by a bacteriologic investigation.

Finally, cases occur in which the exanthem of scarlatina does not present its usual appearance, especially upon some areas of the body, as, for example, the arms and legs—with the trunk remaining almost entirely free—where it shows a coarse macular and partly papular condition, which is common to measles. In these cases the correct course will be indicated by the character of the mucous membrane changes.

The diagnosis may become very difficult if the exanthem shows itself in a rudimentary character or is absent altogether. In the former instance the correct trail can often still be found if it is only not forgotten that the entire surface of the body from head to foot must be minutely examined, especially also the posterior surface of the body, the elbow, the popliteal space, etc.

Where no eruption is present at all, auxiliary circumstances must decide: The circumstances in the surrounding of the patient, the onset of the disease with vomiting, a disproportionately high pulse, etc., and often the later appearance of marked desquamation may show the true significance of the case.

In such cases in which a suspicion is entertained, the condition of the oral and pharyngeal cavities must be observed. The strawberry tongue, the sharply defined, deep red appearance of the velum of the palate, of the uvula and of the palatine arches, the marked deposits on the tonsils, the flow from the nose, the intense swelling and painfulness of the lymphatic glands justify the assumption of a latent scarlatina. The deposits upon the tonsils and the other palatine parts in this form of scarlatina often show an exquisitely membranous character, especially in the first days, so that unless a bacteriological investigation is made, primary diphtheria is much sooner supposed to be present than a diphtheroid. The diphtheria divisions in hospitals are frequently endangered by such cases, namely, by the introduction of scarlatina.

This shows the great practical importance of a correct diagnosis in all questionable cases that have been mentioned, in that the feebly developed, quite rudimentary eruptions, and even those of infections that run a course without rash, are capable of conveying the disease to predisposed organisms, which in the latter may show a severe course and give rise to a fatal issue, and this may occur quite as readily as by the fully developed cases of scarlatina. For this reason the greatest caution is necessary even in every suspicious case.

PROGNOSIS

The general prognosis of scarlatina depends upon the character of the epidemic, which, as has been expressly mentioned, varies greatly in different periods; also in different countries, and in different races, the prognosis is

not the same. In my private practice in Leipzig, lasting for fifteen years, in which I had to do with the district poor, which, therefore, represents the least resistant part of the population, in 358 cases I had a mortality of 13.4 per cent. We must, however, admit in the case of scarlatina that the influence of better conditions of life plays a much less important part regarding the chances of recovery from the disease than, for example, in the case of measles. Jürgensen, in Tübingen, among 547 cases, had only a mortality of 8.23 per cent.; in Stockholm, according to this author, the mortality in different years varies between 2.8 per cent. and 28.8 per cent., upon the average 16.3 per cent.; in England, the mortality varies from 13 per cent. to 40 per cent. In Norway, in ten years, Johannessen found an average mortality of 16.6 per cent. (in children). From these figures so much can be concluded that an individual epidemic, especially in England, may become a calamity almost resembling the most terrible well-known pestilences.

In the individual cases there are very few acute diseases in which it is impossible for so long a time to give a certain prognosis as in scarlatina. This is due to the fact that even in very mild cases the affection at the onset, even at the end of the third week or later, may show a change due to nephritis, which may threaten life or at least produce chronic invalidism. Nevertheless, a regular uniform course—oftener with a well developed exanthem than with a feeble or rudimentary one—during the first week of the disease may be looked upon as a favorable prognostic sign.

Any deviation, no matter how slight, a light rise in the fever, renewed swelling of the glands, etc., never remains isolated but opens the road to all possible serious consequences. Even in private practice rendering a prognosis is greatly facilitated by the keeping of a regular temperature chart: the fever in this instance is a very accurate prognostic indicator. Especial importance should be given to the second half of the first week, in which the first signs of diphtheroid or of otitis media become noticeable, and to the turning point between the second and third weeks, in which nephritis is most liable to occur.

For the prognosis of a severe case with cranial manifestations, three symptoms in particular appear to me to be especially unfavorable: jactitation, dyspnea, with loud respiration, and abnormal frequency and smallness of the pulse (as well as the other signs of cardiac asthenia). Severe stupor, or marked delirium are in themselves by far less dangerous phenomena.

In diphtheroid, the unusually marked enlargement of the glands and the coarse periglandular infiltration which occurs early are very unfavorable prognostic symptoms, as are also a very markedly rising fever, or an otitis media; the prognosis goes hand in hand with the severity of the fever in general.

Finally, in nephritis—at least in most cases—the most certain indicator of immediately threatening danger is the decreased quantity of urine excreted. By the mere estimation of the albumin and also by microscopic investigation of the sediment by no means so accurate an opinion can be gained in regard to the condition as by measuring the daily quantity of the urine. For this reason, even in private practice, we should in no case of nephritis neglect to measure the quantity of urine for each twenty-four hours.

Finally, the age of the patient is not without importance in the individual

prognosis. In the interval from the first to the fifth, and especially from the second to the fourth year, life is mostly threatened by the manifold dangers of scarlatina.

PROPHYLAXIS AND TREATMENT

The prophylaxis of the disease consists chiefly in the prevention of contact between the sick and the well in so far as is possible, and only the diseased human being presents the danger of further distribution. The attainment of this end should be worked for, as the scarlatinal infection need not attack every person who is exposed to it, for the susceptibility to the poison decreases with advancing years and, on the other hand, every infection may lead to a malady dangerous to life. This course is more easily prescribed than carried out, as, especially in families with many children closely crowded together, the separation of the sick from the well is often quite illusory, but even among the better situated classes of the population there is great difficulty with this prophylaxis, as the disease, especially in adults, appears in a form which is not readily recognized, showing but the usual angina, but which fact does not materially interfere with the transmission of the disease. Just this circumstance, however, makes it our imperative duty to prevent contact of those around the scarlet fever patient with others free from the disease, thus, they should not be allowed to go to school, to infantile institutions, kindergartens, hospitals, etc. Difficult as it may be for the affected family, the brothers and sisters of the scarlet fever patient must remain isolated during the entire time of the disease. In many countries this is required by law.

The question is often asked of the physician whether the healthy nurses or relatives of the child may visit other families, may receive company, travel, etc. Particularly in regard to the possibility of the transmission by the healthy, or at least apparently healthy, I would advise prohibiting this. Transmission by the physician from one sick-bed to another or to his own family is not likely as the visit of the physician to the bedside is usually a very brief one and a sufficient quantity of poison does not adhere to him. If only he does not have a latent, unsuspected scarlatina himself! Yet the greatest cleanliness and care is absolutely necessary even on the part of the physician. Wherever possible, his visits to patients of this kind should come at the end of his visiting list, and the custom which is coming into vogue of covering the clothes with a linen gown in visiting the sick should perhaps be generally introduced.

Particularly difficult and important is the question of disinfection of the sick-room after termination of the disease. This involves great inconvenience and often enough decided injury to the infected individual, and also in not a few cases its value has been shown as illusionary, and we must actually admit that it has not been strictly proven that the poison of the disease may adhere to the sick-room in a condition capable of further dissemination. In most cases of this kind, when the disease has terminated (for example, by death) and the poison has still shown itself to be active, there remains the possibility that it has been present in the oral cavity of a person who has been active about the patient. Nevertheless, in view of our present knowledge of

the nature of the scarlatinal poison, it is perhaps impossible to avoid unnecessary measures.

All these difficulties could to a great extent be avoided if in every case of scarlatina (as also in other infections), instead of sending away the well children as is usual, the entire population would agree to send away every sick child after the disease has been determined with certainty. In order to carry out this plan it would be necessary to have more well-equipped hospitals for treatment of contagious diseases than exist at present, as do some other countries (America, England, Denmark, Sweden). Where these opportunities exist they are at present largely shared by the rich and the poor, this being shown by the experiences in Stockholm, with the new infectious hospital erected there, and I have also observed this since the erection of the new Children's Hospital in Leipzig. With increasing frequency, the first families of the city come with their children sick of scarlet fever or diphtheria to the hospitals to have them treated there. Especially in regard to the better situated classes, it is necessary, in the erection of such hospitals, to make it possible that the mother may accompany her child. Yes, even more. The families should not be required in such cases to give up their physician who has perhaps been attending them for years for one who is unknown to them, nor should the dignity and position of a thorough family physician be sacrificed by allowing his patients to pass into the hands of any other physician. I see the solution of the dilemma only in this, that, according to the example of the many sanatoria which exist in large cities, in which infectious patients are taken, every practising physician should be allowed to continue treating his patients with or without the cases being accompanied by relatives. Nothing is changed but the sick-room. Transportation among the first hours or the first few days of the disease is always possible. In the course of time a system of this sort is bound to develop.

That, naturally, there should be a disinfection of all utensils and objects which have come into contact with the patient, bed, toys, etc., which may be contaminated with the poison, and are, therefore, dangerous, is clear. They should be disinfected and if possible destroyed. It is impossible to enter here more minutely into these hygienic questions.

Simple scarlatina has a typical course which so long as we are not in possession of a specific remedy had better not be disturbed by interfering measures. The object of the physician consists in the widest sense in ordering the diet and in superintending the nursing. The patient in most cases goes to bed of his own accord and even in the milder cases should be kept there for at least three weeks and not allowed to get up, until by a careful examination of the urine which has been saved for twenty-four hours it has been shown that the kidneys have been spared. This indication should be carried out under all circumstances.

Wherever possible—even in small dwellings—the patient and the nurse should each have a room. The rest of the family during such an unfortunate time must make up their minds to suffer some inconvenience. In better situated circles wherever possible two neighboring rooms should be used. As soon as the disease has been recognized the physician must prevent the other

children from going to school. What a calamity this is, in the narrow rooms which often represent living room and kitchen in workmen's dwellings, may be imagined. I have had some experiences which would scarcely be believed. Therefore, in such instances it is our duty to use all our influence toward sending the sick child to a hospital. Naturally, often enough the money question is in the way, provided the case occurs in a family that has recently come to the city (in Germany). The patient must not be allowed to have company.

The sick-room is to be kept rather cool than warm, from 64° F. to 68° F. is sufficient. The covering for the fever patient is to be light. The child is to be supplied with fresh body linen and bedclothes, which during the disease must be carefully (previously warmed) renewed. The nutrition in the first three weeks should consist of a pure milk diet which may be varied in many ways (adding some coffee, bonnyclabber, buttermilk, rice and milk, milk and grits). The assumption that by these means the development of nephritis may be prevented is erroneous, but it is possible that by a too early administration of food containing extra amounts of albumin the kidneys may be irritated and nephritis caused in this manner.

The skin as well as the mucous membranes must be kept scrupulously clean; wherever possible, and especially if the children are accustomed to it, the patients are to have a quick luke-warm bath daily. In other cases the face, hands and feet, and any soiled parts of the body are to be washed with luke-warm water and soap. Especial attention is to be given to the daily cleansing of the nose, by cotton tampons which have been moistened, and the careful washing of the mouth and pharyngeal cavity, and by frequent active or passive cleansing, such as gargling with a luke-warm, dilute salt solution. This is to be repeated five to six times daily. It is advisable to use cheap substances such as cotton or the like, which immediately after use may be collected and burned.

For the thirst, dilute acid drinks, lemonade or the like or boiled water with a little citric acid and sugar, are given. Internal medication is quite unnecessary. I am decidedly opposed to the early use of antipyretics, those from the group of benzol derivatives. Only apparent success is attained and the regular course of the disease is disturbed. Where there is a necessity for influencing the fever, a plentiful amount of cool drink (but without the addition of alcohol) should be administered, and there may be cool applications of towels doubly folded and moistened and applied upon the chest, abdomen, and thighs, these being covered by woolen cloths. These applications may be readily fastened around the abdomen by means of bandages. In marked coma and severe delirium one or two, perhaps more, luke-warm baths are given at a temperature of 91.5° F., with cold affusions. The technique has been described in the treatment of measles. During the period of desquamation, this is favored by luke-warm cleansing baths. In cases in which there is marked itching or burning, inunctions with washed lard which were formerly so much used may be employed or a 1 per cent. thymol-lanolin salve may be of value.

Thus, convalescence is awaited and only the course of the temperature is carefully observed so as to be prepared for threatening danger.

If such dangers develop, prompt interference is necessary even in desperate cases, if only to give the parents the satisfaction of feeling that no measure that is known to professional skill has been neglected in the attempt to save life.

Before entering upon the discussion of the treatment of the individual varieties of anomalous scarlatina, a few remarks regarding *general treatment* which influences the scarlatinal process may be in place.

The most important is the attempt to introduce a serum therapy. This depends upon investigation showing that the recovery from scarlatina confers immunity toward the infection for the one that has recovered; this immunity is referred to the presence of antitoxins in the blood of the convalescent. As well as in the case of the animal that has been inoculated with diphtheria, in which the antitoxin-containing blood serum shows a curative action, so also the serum of a scarlatina convalescent is said to remove the dangers of blood intoxication due to the scarlet fever attack. It is clear that this serum therapy is erected by hypotheses and should not be mentioned in the same breath with the accurately determined diphtheria serum therapy which has been proven by experiment. We are not familiar with the scarlatinal poison, we do not know whether it forms toxins, nor whether the scarlet fever immunity is due to the permanent presence of antitoxins in the blood. And even if this were the case it would be very questionable whether small amounts of the blood of convalescents which contain so much antitoxin would combine the hypothetical poison in a second organism. It must be remembered that in the case of diphtheria, the animals which furnish the antitoxin have been exposed to an enormously increased severe infection before their blood shows curative properties. Thus, theoretically, the thought of serum in the therapy of scarlet fever in its present condition does not promise very much. I should believe that trials would only be justifiable in those desperate cases in which all other previous measures have proven ineffective. In these cases every rational attempt is permissible.

Another general treatment has recently been advised by Seibert¹ in New York: Repeated inunctions of the entire body several times daily with a 5 per cent. to 10 per cent. ichthyol-lanolin salve. Every six hours the entire surface of the trunk and the extremities is, with slight pressure, to be anointed; in each inunction, according to the size of the patient, 30 to 90 grams are to be used. I have employed this method quite frequently, most children bear the inunctions very well and sometimes it appears to influence the temperature and general condition of the patient. The method is quite difficult, requires much body linen and is very expensive. Of actually severe cases, none have been saved by it, for this reason I have abandoned the treatment. Kraus reports from Ganghofner's clinic, rather an exacerbation of the cutaneous affection by the ichthyol inunction. I have not observed this.

Nor have I seen success from inunctions with Credé's argent. colloidal nor from the subcutaneous use of Marmorek's streptococcus serum. Wherever the treatment has been carried out, it was unsuccessful in a number of cases before being abandoned.

¹ Jahrbuch für Kinderheilkunde, Bd. li, p. 308, 1900.

Thus, until now the hope of a successful treatment of the *indicatio morbi* has not been attained.

We shall now turn to those measures which have shown themselves useful in the individual cases in which complications have arisen.

The treatment of *scarlatina gravissima*, according to my experience, is entirely hopeless. I have never seen a case recover in which the diagnosis was at all certain; the strongest *analeptica* (up to 1.5 grams camphor subcutaneously in twenty-four hours), antipyretics, hydrotherapeutic measures, are of no avail here; nevertheless, in every instance the attempt must be made to combat the disease with all the energy at our command, and, besides, some cases which are characterized by especially intense fever and severe nervous symptoms resemble the severest form, although they are favorably influenced by the remedial measures now to be named.

Above all, the cooling and stimulating effect of the water treatment must be considered. The very rapid rise of the body temperature to a great height, which in itself is dangerous, requires a purely symptomatic withdrawal of heat. I cannot advise the employment of cold baths for this purpose. I used them formerly but I find that the infantile organism upon the whole does not bear them well, and that in the case in question, in which there is almost constantly a cardiac weakness present this is a *contra-indication*. I prefer for this purpose repeated packs, the influence of which may be extended to an hour, without causing a decided internal congestion of blood as is the case with a cold bath. For this purpose two beds, each supplied with a sheet and woolen blanket, are necessary. The cover and the sheet, which have been wrung out in cold water, (at 59° to 60° F.) are spread out, the naked child is enveloped up to the neck, first in the sheet then in the woolen blanket, and allowed to remain so for ten minutes (or if the hyperpyrexia is not so marked, for fifteen minutes). In the meantime the second bed has been prepared in a similar manner and the child after it has been taken from the first pack is immediately enveloped in the second for ten (up to fifteen) minutes, and so forth for an hour, so that the decided cooling is repeated from four to six times. The difference between this method of cooling and a cool bath are obvious enough; between the renewed coolings the sheet warms itself inside of the woolen covering and the blood remains upon the surface of the skin. The result of the cooling is very energetic. This procedure must not be employed more frequently than two, or at most three times a day. In the intervening periods the child is to be allowed to rest.

Secondly, in those cases in which there is marked nervous implication, *cold affusions in a warm bath* are of use. The duration of this (temperature 90° to 95° F., according to the condition of the pulse) may be five, ten, or even fifteen minutes (in older children), but may also be very much shortened. The principal indication here is the cold affusion. The children are comfortable in the warm fluid, which, compared with the temperature of the body, is always 12 to 15 degrees lower, and now the beneficial contrast for the nervous system, the cold, "the cold shock" occurs. From a slight height water cooled by ice is poured over the head, neck, back, and chest, in short intervals according to the length of the bath; at least 5 to 6 litres are to be used. The external auditory meatus is to be closed by plugs of cotton. The

parts of the skin upon which the cold water is poured are to be gently rubbed during this procedure as well as the trunk and extremities which remain in the bath. Each affusion causes deep respiration that cannot be attained by any other method, therefore, a very decided area of the lungs is influenced. Quite a number of other reflexes also occur. The effect upon the centres in the medulla cannot be mistaken. The baths are repeated four, even six times daily. Usually after this procedure children will take a larger quantity of nourishment, which is followed by quiet sleep.

A third process has for its object combating the cardiac weakness. Here, in my opinion, alcohol is absolutely necessary. Strong, old red wine, and especially champagne, stimulate the cardiac and vasomotor activity so long as the greatest danger appears to be present. After this has passed the alcohol may be discontinued. But during the storm of the life-threatening symptoms, it is well not to be too sparing with it. Other analeptica are to be utilized at the same time, especially camphor, which in an oily solution may be given hypodermically every two hours or even oftener. Of a 20 per cent. solution, according to the age, I give from one-half to an entire Pravaz syringe-ful per dose.

By French authors (Moizard) the subcutaneous injection of caffein (10 per cent. solution of sodium salicylate of caffein, one-third to a syringe-ful to a dose) and where the nervous symptoms, besides asthenia, are especially developed, sulphate of spartein (4 per cent. solution, one-third to one-half syringe-ful to a dose) is advised. I have had no personal experience regarding these procedures.

The treatment of *diphtheroid*, above all things, requires a frequently repeated cleansing of the oral, nasal and pharyngeal cavities. Even the simple, frequently repeated drinking of pure water, or water containing some acid fruit syrup, is of value; but drug treatment must be added. There are a large number of disinfectants which may be used in solution, as a gargle or mouth wash, or may be insufflated into the mouth and nose. Boric acid (5 per cent.) is a favorite, but is not especially active, also salicylic acid (1 to 100), or hydrogen peroxide (3 per cent.) may be employed. In the last few years ichthyol has appeared to me to be of especial value. I use it almost exclusively in the form of a 5 per cent. solution of ammonium or sodium sulphoichthyolicum. I have used it much in private practice and have heard many physicians praise it. The disagreeable taste of the solution is unpleasant, so that some very sensitive children object to it; usually, however, this repugnance can easily be overcome upon the second day. The application occurs in older children in the manner that after washing or gargling with pure luke-warm water (to remove the mucus masses or remains of food) the same process is repeated with the ichthyol solution. In younger children the same object is accomplished by means of a tube, syringe or irrigator. This process has the advantage that under all circumstances the disinfecting fluid also reaches the posterior and lateral pharyngeal wall, which is not the case with simple gargling.

The syringe must not be used through the nose, but a small quantity of the disinfecting solution may be poured into each nasal opening by means of a spoon or the like, it is then allowed to flow out by the mouth; small quanti-

ties are naturally swallowed. Or a tampon of cotton, having been dipped in the fluid, is pressed out in a similar manner as was described in the chapter in the treatment of measles. Previous to this, each half of the nose is to be cleansed, as carefully as possible, by means of small pellets of cotton. For nasal disinfection, insufflations are also valuable, for example, of the sodium sozodol powder mentioned under measles. By these remedies the surface of the diseased mucous membrane may always be denuded and thus prevent the increase of the dangerous streptococci.

If, however, necrosis of the mucous membrane has occurred in extended areas in the naso-pharyngeal space, these septic microbes are no longer in reach of superficial washings for they are already proliferating in the deeper tissues.

We even now possess a method of reaching them or at least of causing some attenuation, even if not destroying them, in the subcutaneous injection of antiseptic remedies into the palatine areas, a 3 per cent. carbolic acid solution being best for this purpose. The object of this treatment is not to influence the diphtheroid locally but to introduce these solutions into the roots of the lymph vessels which lead to the lymphatics of the lower jaw. The antiseptic is to take the same road which the mass of septic streptococci takes as well from the nasal as from the oral cavities, and to meet them in the lymph vessels and lymph glands and render them harmless. The proposal for this method of treatment, which I mentioned in 1886, has been accepted by a number of pediatricists, who like myself were satisfied by the results attained. Its general introduction into the treatment of scarlet fever has not yet taken place, but I have used this method for over twenty years and have not given it up, for it appears to me that it is more valuable than anything else that has been tried. For the injection, a Taube cannula is employed; this is attached to a Pravaz syringe, injections being made twice daily into each half of the palate (tonsil and anterior velum of the palate, arch of the palate), half a syringe of being employed, therefore, in all 0.6 phenol daily. The manipulation in this process is easier and simpler than the previously used method of making applications to these parts. If a brown color of the urine occurs this treatment is stopped. The method is begun as soon as the rise in the temperature, which was mentioned in the clinical description, takes place, upon the fourth or fifth day, or an increase in lymphatic enlargement, etc. announces the danger of diphtheroid; under some circumstances, in severe cases this treatment may be begun upon the first or second day. It is continued until the glands become smaller, the fever declines or the condition of the oral and nasal cavities shows a tendency to limitation of the inflammatory necrosis. Not rarely more or less extensive necroses are found in the surroundings of the openings made by the needle. These are not caused by the carbolic acid itself, but are due to the severity of the local affection and may appear in the same intensity in areas in which no injection has been made. If necroses occur in wide distribution around the point of insertion I stop the injection in the infected half of the palate. In themselves these losses of substance, as has already been explained, are rarely of danger.

The inflammation of the lymph glands, which very often takes a substantive character, may be controlled at the onset by application of ice. If,

however, marked enlargement, hardness, or periglandular infiltration have taken place, then a warm poultice is more valuable to produce suppuration as early as possible so that an incision may be made. The incision of non-suppurating necrotic glands as well as the excision of numbers of such infectious glands has as yet not been followed by favorable results. Regarding inunctions of mercury salve, of argent. colloidal, I have seen no other results than that they make the skin dirty and not infrequently produce excoriation. I leave the cutaneous coverings of these septicly affected parts alone. Analogous to this a purulent parotitis should be treated. I have never seen this complication in scarlatina.

Of greatest importance, besides the local treatment of the scarlatinal diphtheroid in the mouth and nose, is the attention which must be paid to the condition of the middle ear. The same is true here as was mentioned in the discussion of measles, which was accurately described and for this reason need not be repeated.

Scarlatinal rheumatism is treated with the same symptomatic results as is polyarthritis, by antirheumatic remedies. I have not seen a justification of the fear that by their internal use the kidneys would be injured. Among 29 cases of scarlatinal rheumatism in my practice, 3 later suffered from nephritis. This is exactly the same percentage which was observed in the total number of cases. At that time the rheumatism was almost exclusively treated by salicylic acid. Now it is better to use the milder and more pleasant *aspirin*, but not in too small doses (afternoons at two, four and six o'clock doses each of 0.5 ($7\frac{1}{2}$ grains)). As a rule two days of treatment is sufficient. The less severe cases may be treated by keeping the affected joints warm, the symptoms disappearing from them in from four to six days.

In postscarlatinal fever, the ear and the posterior pharyngeal wall are to be carefully examined, regarding a possibility of absorption of septic material, the treatment being accordingly. Ichthyol washings of the posterior pharyngeal wall from the mouth render good service.

Scarlatinal typhoid is to be treated in the same manner as a mild attack of infantile enteric fever. There should be employed cool packs to the chest and abdomen, cool drinks, under some circumstances baths and drug antipyretics, but here, above all, quinin may be utilized.

Scarlatinal nephritis in a great number of cases may take the simple course described and in the main requires but simple dietetic treatment. It is good practice so long as the amount of urine does not fall below 500 to 600 cc. to desist from active treatment. Milk diet is continued; and by all possible auxiliary measures (addition of some coffee or tea, with variation in the form of buttermilk, etc.) an attempt must be made to give as much of this food as possible (2 to 3 litres), so that the requirements of the body are completely covered. Besides milk, luke-warm drinks may be given (lemonade, tea) or some alkaline mineral water, but if at all possible there should be no other food substance so long as a sufficient quantity of milk can be taken. In those cases in which milk cannot be administered, which are not frequent, the food should consist particularly of vegetables; wheat bread with butter, dried or fresh vegetables, fruit soups, cereals, fruits. Many of these substances may be prepared with milk and will be taken by those that reject pure

milk. But the action of a mild diuretic, which milk if it be taken alone shows, cannot be attained in this manner. Occasionally small quantities of milk will be taken frequently instead of large quantities at one time.

The fever which occasionally accompanies nephritis need not be especially considered in the treatment, particularly as it is of brief duration.

As soon as the urine secretion falls below 400 cc., showing a more decided injury to the kidney, active measures are necessary. With regard to the marked implication of the vascular system in the damage to the scarlatinal kidney, I hold that every measure which may produce an irritation is a two-edged sword, and prefer for this reason to spare the kidney in the acute stage. Even mild drug diuretics, as for instance potassium acetate, I do not employ, for I allow this function to be carried out by food and by drink. I prefer to make the skin active and to withdraw water by means of sweating. The best method consists in placing the patient in a warm to a hot bath (95° F. gradually rising to 100.5° F.), this lasting from ten to fifteen minutes, and being followed by dry or moist packs. In cases in which fever is present the sheets may be dipped in cool water so that heat may be withdrawn at the same time and even the bath may be cooler. The patient is allowed to remain one-half hour in the pack after profuse perspiration has appeared in the face. Then the covers are gradually removed, the skin is dried with warm cloths, and the patient is placed in the bed which has been previously warmed. This process is only to be carried out once daily. There are, however, children who in this manner at least cannot be caused to sweat, especially in the beginning, then warm tea may be taken during the pack; and in cases in which this does not act I have very often with advantage given a little pilocarpin. The subcutaneous injections of this remedy have been quite properly abandoned, but small doses internally appear to me to be but slightly if at all dangerous. At the onset of the pack the child is given 10 grams of a solution of 5 centigrams of pilocarpin to 100 grams of water. Almost always, shortly afterward, slight vomiting and salivation occur and the enveloping material should be protected by a cloth which is placed before the mouth; soon afterward, however, sweating takes place. Frequently this method need be used but once, sweat following later without the use of the drug.

In a favorable action 300 grams of fluid may be withdrawn from children, frequently, however, not more than 60 to 100 grams. As, however, according to Strauss,¹ the molecular concentration of sweat is decidedly under that of blood serum it is always a question whether by this procedure an absolute substitute of the renal function in regard to the removal of urinary substances is attained. On the contrary, it might be questioned whether the mere withdrawal of water would not rather tend to increase the concentration of the blood serum, producing an unfavorable action, in that uremic symptoms would be more rapidly produced. In fact, every experienced physician has seen one or the other example of the appearance of uremic phenomena soon after a hot bath or a hot pack. But these are for the most part rare exceptions, whereas usually a subjective and objective amelioration follows the

¹ Fortschritte der Medicin, Bd. xix, Nr. 21.

procedure. However, the experience just described makes it necessary to watch the patient after this sweating process has been attempted, in order to note the momentary success. Perhaps the undoubted frequent use of this measure does not consist in the withdrawal of water but in the regularly marked flow of blood to the skin, in which way the main object is attained.

The value of depriving the renal circulation of blood by *direct withdrawal*, with an increased experience, has become more and more unquestionable to me, so that I should like to advise this method of treatment rather than that in which sweating is produced. As soon as, with a decline in the excretion of the urine (immaterial whether this contains much or little blood), the first symptoms of intoxication occur, i. e., headache, vomiting, I lose no time but apply to each renal region, according to the age of the child, one or two leeches. The succeeding bleeding is to be kept up for a little time afterward. Sometimes I have seen that it has been rather severe and continuous so that compression or other measures were necessary to stop the hemorrhage. However, it is better when a little too much than too little blood flows. The leech itself withdraws about 10 grams of blood and if (with 2 leeches), therefore, a similar quantity, 15 to 20 grams, flows from each wound, this is of advantage. Soon afterward, in favorable cases, the secretion of urine rises again, and headache and nausea disappear. In the severer cases, however, the improvement is not sufficient, it is transitory, and headache returns. Cloudiness of the sensorium and a convulsive attack are added. Then without more ado there should be general blood-letting by means of *venesection*, by which 100, 150, or even 200 grams of blood in older children, may be withdrawn. I have gathered quite a number of observations in my clinic as well as in my consultation practice in the last two years, in which venesection has been followed by life-saving success. This may be followed by a subcutaneous injection of a normal salt solution of 100 to 150 grams directly. The secretion of urine is permanently increased; it is still bloody for some days, but is copious; the convulsions do not return and the beginning amaurosis gradually disappears.

If in a severe scarlatinal nephritis the kidney is examined then, with the extended stasis of the blood in the glomeruli, in the cortical capillaries, in the vasa recta, the connection is not very difficult to understand. Without increase of blood pressure, by means of the general diminution of the amount of blood, the renal blood channels can be more readily traversed. Besides, perhaps the removal of a part of the retained substances of the blood serves a further purpose. It may therefore be a condition which allows the organism to return to a normal state. A certain advantage is attained by the use of warm poultices in the renal region.

After the danger of uremia is over, or at the same time with it, it is necessary to combat the cardiac asthenia in severe cases. Even the subcutaneous salt infusion is of value here. But the question arises, whether drugs should be used. Here, with rapidly approaching danger, camphor, even in repeated large doses, is valuable, but more frequently instead of combating a rapid collapse we must treat a permanent and slowly advancing asthenia. Regarding the favorite method of treatment by digitalis, at least so long as the case is in the acute stage, I have an aversion, which is perhaps not justi-

fiable, but which is based upon a momentary increase in injury and a fatal ending in a previous severe case of nephritis. Care in the employment of this potent remedy is necessary under all circumstances.

Steffen advised in these cases of cardiac asthenia to administer ergot in fair-sized doses, three to four times daily. I followed his advice and employed the fluid extract. In fact it appeared to me to be occasionally useful in combating the dilatation which gave rise to cardiac weakness.

Occasionally the subcutaneous injection of *strychnia nitrate* once daily has a beneficial influence upon the cardiac activity.

Caffein should also be considered, as it shows a simultaneous action, as a stimulant for the weakened heart muscle and as a vasomotor remedy. Naturally, also on account of the simultaneous influence on the kidney, the remedy must be given guardedly.

Then by plentiful nourishment the action of the heart may also be restored. According to the investigations of v. Noorden, no great fear need be attached to the administration of other albumins than of the casein of milk, as was thought to be the case formerly. It is best in nephritic cardiac weakness to arrange the diet so that, with moderate quantities of albumin, carbohydrates are also mingled with the food. The treatment of these conditions requires the greatest care as well in the choice of a drug as in a nutriment.

[See also Serum Therapy, page 909.]

SMALLPOX, VARIOLA

By CH. BÄUMLER, FREIBURG

THERE has been no opportunity of observing variola in any form in this clinic for nine years; still it is necessary for every well-informed physician to have a knowledge of this important disease. As a result of strict vaccination and re-vaccination, in Germany, the disease has been prevented from appearing, so that many physicians have never had an opportunity of seeing smallpox. However, on account of our great intercommunication with other countries, we may at any moment be required to treat the disease in travellers, for in many European countries the protection by vaccination is not very effective and the disease occurs more frequently than in our country, owing to the absence of strict laws. Especially in cities situated on the boundaries, as in Freiburg, this may readily happen. All cases of smallpox that have been treated in our clinic in the last thirty years, in the smallpox hospital, now called "Emergency Hospital" have come from Switzerland or from France.

The last case of this kind was especially remarkable. A woman aged thirty-six, having a small store in Berlin, travelled with her nine-year-old son to Lucerne, Switzerland, to recuperate. Upon her return, on May 15th, 1893, she took a room and on May 20th was attacked by fever. On May 22d an eruption appeared, and, as the disease of the woman increased in severity, a physician was sent for, who, only a few days later, when the eruption became pustular, became suspicious that he was dealing with smallpox. Only on May 29th, at a time in which the eruption was fully developed, was the patient sent to the smallpox hospital. The eruption was confluent in the face, and the patient showed evening temperatures of 102.4° F. Not until the eighteenth day of the disease was the patient free from fever and on June 27th she was able to leave the hospital. The son, in spite of the fact that he was with his sick mother for nine days and slept in the same room, did not develop the disease. Apparently he was still protected by vaccination in his early youth; in the mother, however, who was also vaccinated in early childhood, the protection was no longer sufficient. She must have contracted the malady about May 10th, in Lucerne, and she showed quite a severe form of the disease.

Of the persons that came in contact with the patient in her dwelling, none were affected. All those who in any manner came in contact with her after the disease had been recognized were vaccinated.

Upon a former occasion, in 1880, a student, who had attended a demonstration of a mild case of variola, in a patient who came from Bern, was attacked by a medium severe form of the disease (For fever curve of the case, see below), so that he retained permanent scars in the face. The patient in question was first admitted to the surgical clinic, as he had injured his tibia eight days previously. As headache and fever developed the first night, he was transferred to the medical clinic, where, upon the following day, two days after the onset of the fever, the eruption which began to develop showed the true nature of the affection. In spite of the fact that the patient only remained

for twenty-four hours in a very large, well-ventilated ward of the medical clinic, one of the inmates of the ward developed a mild form of the disease, although all the patients were vaccinated.

That we must always be on our guard in Germany is proven by 4 fatal cases among 27, in an epidemic which occurred in Frankfort-o.-M. in June and July, 1900.¹

In 1902, in various cities of England, especially in London,² there was quite a severe epidemic. On February 15, 1902, in London alone, there were 1,185 cases in the smallpox hospitals, and in Glasgow in Scotland at the same period 133. If we consider the great travel between England and the continent, and that the laws regarding protection by vaccination are less strict in Belgium, France and Switzerland, it will at once become clear why we must always be upon our guard. In the rapid transit of these times, inside of one week a traveller may easily come from New York to the heart of Europe, and, being ill, may consult a physician in Germany; it will then be necessary to decide whether or not smallpox is present. Every physician should, therefore, do all in his power to become thoroughly acquainted with the affection, especially regarding prophylaxis and vaccination.

ETIOLOGY

Up to the beginning of the nineteenth century, smallpox was the terror of mankind. Next to the plague, it was the most destructive pestilence of humanity. Even in the eighteenth century in the various countries and cities of Europe including also Berlin, 8 per cent. of the entire mortality was due to variola, high and low being attacked to the same extent. That these terrible devastations, which particularly raised the mortality of infancy, have now ceased, we owe entirely to Jenner's discovery of vaccination. Those who desire to inform themselves regarding this question, I may refer to the book published in the year 1870, "20 Letters Regarding Human Smallpox and Cowpox Inoculation," by my predecessor, Kussmaul.

Where smallpox originated is enveloped in doubt, it is very probable that it had existed in Eastern Asia for a long time before it was brought from there to Europe. It is absolutely certain that it appeared in Egypt about the middle of the sixth century of the Christian era. From there the disease found its way to Constantinople and thus gradually gained a foothold in Europe. It was brought to America by the Spanish.

The Arabian physicians, especially Rhazes (850-932?) were the first to give an accurate description of the affection. But in earlier times variola was confounded with all other possible eruptive diseases; the French name "petite vérole," to differentiate it from "la grande vérole," syphilis, as well as the synonymous English term "smallpox" indicate this. Th. Sydenham (1624-1689), was the first to separate variola from measles. At the present time, when we observe so much more accurately and are less influ-

¹ Münchener med. Wochenschr., 1900, No. 50.

² A very instructive study regarding the distribution of smallpox in England is given by A. Gubb in the *Semaine méd.*, February 5, 1902.

enced by theories, it appears strange that a disease in which the body and especially the face, is covered with pustules, should be confounded with another in which the eruption consists principally of bluish-red papulo-macules, and only exceptionally upon the trunk shows minute sudamina. Very probably in former times, perhaps due to the methods of treatment in eruptive diseases and in febrile affections in general, as the result of sweating and uncleanness, there were added to the original eruption other inflammations of the skin which became purulent. Thus in an advanced stage of the malady it may have been difficult to decide what belonged to the original affection and what was superadded.

In what manner preconceived opinions and theories may take possession of even the most advanced minds, is seen from the fact, that the marked transmissibility of the affection from the sick to the healthy was only determined by Boerhaave (1668–1738). This may be explained in the manner that in the regions in which the disease had once gained foothold, it never disappeared completely, so that there were sporadic cases in which the transmission from case to case could but rarely be traced. The influence of the stars and atmospheric conditions were sufficient in those times to explain the appearance of pestilences. Have we not seen similar conditions in our times in explaining the chief cause of another epidemic disease, influenza? Although Haygarth and Falconer during the pandemic of influenza, in the year 1775, defended the opinion that influenza was a disease which spread by contagion, upon the basis of very careful observations, only in the last pandemic of 1889–1890, did the old view that a miasm and atmospheric conditions produced and disseminated the malady lose ground, till, finally, in 1893, Pfeiffer discovered the infective germ. In both diseases it was the proof of human intercourse which influenced the distribution of the affection, which became determining for the assumption of the transmissibility from the sick to the well.

In variola we are dealing with an *eminently contagious disease*, the *pre-disposition* extending to all individuals and to all races, and to all ages, but being especially great in young children. Nevertheless, some few instances of hereditary immunity are known. The case of the celebrated physician Boerhaave was one of these. It has been assumed that such persons have passed through the affection *in utero*, without traces having been left upon the skin. Several observations have shown, however, that even such persons as appear to be immune, who for years may act as nurses, being exposed to contagion without becoming ill, finally, in old age are still liable to attack. As in other infectious diseases, so also in variola, the susceptibility of the individual is not always the same.

Variola in the mother is soon transmitted to the fetus, sometimes this is not the case. This appears to be in connection with the blood-vessels of the placenta. Mothers having smallpox may give birth to children that either show the well-developed eruption or the scars of a past eruption, or, on the other hand, children who are entirely free from the eruption. Whether children of the last-named variety are immune to later attacks of variola, has not been determined with certainty, but it is likely. In smallpox hospitals they are vaccinated soon after birth to ensure certainty.

Recovery from an attack of smallpox conveys a high degree of immunity

from future contagion. This protection is not absolute. In the smallpox hospital in London, from the years 1836–1851, among 5,797 cases, 47 cases occurred, therefore, less than 1 per cent. of second attacks. Even fatal second attacks have been observed. As a rule, however, such second attacks are milder, the organism being influenced by the previous attack.

A still more effective protection from contagion is conveyed by the successful inoculation of cowpox, by “vaccination,” in early childhood and repetition of the process at puberty, and, later, whenever there is danger of contagion, “re-vaccination.”

Transmission of variola to animals (monkeys, domestic animals) is possible. In certain domestic animals (cattle, sheep, horses) similar affections, resembling human variola, in regard to the eruption, and, in some animals, even in respect to the constitutional phenomena, are seen. In the sheep an epidemic disease is observed in which the eruption distributes itself over the entire body (variola ovina); in horses and cattle the eruption is localized to distinct areas; in the horse to the fetlock joint region, in cows to the udder. This local variolous affection runs its course without marked constitutional symptoms.

“*Cowpox*” (vaccinia) now and then is transmitted to the hands of those milking the cows, and then runs a course at the point of transmission, as a local cutaneous affection. The laity had variously observed, that persons who in this manner had contracted cowpox naturally did not contract human smallpox even if exposed to it. This condition was observed by Benj. Jesty, in 1774, in England,¹ and was utilized in numerous successful artificial vaccinations; the same was done by Plett, a teacher in Schleswig-Holstein (1792).²

It remained, however, for the physician, Edward Jenner, of Berkeley, in the West of England, to foresee the importance of these experiences and he utilized them in a systematic manner, in forming a protective inoculation measure against smallpox. A boy vaccinated by him from the cowpox which had appeared in the hand of the dairymaid, Sarah Nelmes, showed the usual signs which arise from accidental transmission and the boy proved upon subsequent inoculation, upon the first of July of the same year, with smallpox virus to be insusceptible to the disease. Upon inoculation later on the same condition prevailed.

By the protection which the recovery from cowpox conveys toward human smallpox, the close relationship of the two diseases to one another is shown. But it is very remarkable that a disease which remains localized to the skin at the point of inoculation shows a similar influence upon the entire organism to that of recovery from a severe general affection with an eruption over the entire body, and which may even be transmitted by the air as is the case with human smallpox.

The *cause of the disease* has not as yet been determined with certainty. In the pustules of the pock in man, as well as in cowpox, there are found

¹ British Med. Journ., December 14, 1901.

² Jos. Jones, Contagious and Infectious Diseases, Measures for their Prevention and Arrest. Circular No. 2. Extract from the Report of the Board of Health of the State of Louisiana, Baton Rouge, 1884, p. 173.

small, feebly refractive organisms, which, according to Guarnieri, multiply when transmitted to the cornea of the rabbit. v. Wasielewski¹ succeeded in cultivating these "vaccine-bodies" in the cornea of the rabbit through 46 generations. With Guarnieri, he believes them to be cell parasites and the causative agents of cowpox. L. Pfeiffer, in Weimar, in the year 1887, described protozoa in the contents of human smallpox and in cowpox.

[Ewing has lately published a preliminary report of his researches in 29 cases of smallpox with reference to the pathological anatomy and bacteriology of the disease. The skin lesions reveal the presence of vaccine bodies in all stages of their development, the numbers of these bodies being proportionate to the hemorrhagic character of the lesions. Streptococci were present in all the specific lesions at a very early stage, frequently in enormous numbers; sometimes they could not be detected at all in the smears of the vesicles or pustules. The next most common bacterial form was a fine bacillus resembling a minute Klebs-Löffler bacillus. Ewing states that, at the present time, while it hardly seems possible that the streptococcus is the specific contagium of variola, one cannot fail to be strongly impressed by the fact that this micro-organism is present at all stages of the disease and in numbers proportional to the severity of the attack. It is difficult to reconcile the principles governing secondary infection by streptococcus with the presence of this bacterium in the blood during life, and with its enormous numbers in the blood shortly after death in the primary hemorrhagic cases. In these cases the streptococcus completely overshadows any other bacterial agent that may be present, and the idea of a secondary infection in such cases does not seem reasonable. He believes, therefore, that the condition in these cases should be regarded rather as a symbiosis of the streptococcus and the specific agent, from a very early period, so early as to be indistinguishable in these cases from a primary invasion. While not inclined to urge that the streptococcus is the specific agent in variola, he believes that it will always remain impossible to reproduce the disease, especially the fulminant types, without the presence of the streptococcus.

Councilman, Magrath, and Brinckerhoff have recently directed attention to the original observations of Guarnieri on the supposed parasite of smallpox and later important works of Wasielewski, and given the results of their own studies, stating that in the lower layers of the cutaneous epithelium, before there is any anatomical evidence of vesicle-formation, small structureless bodies, 1 to 4 microns in diameter, may be found lying in vacuoles. The larger of these bodies are irregular (suggesting an ameboid character), and they may become as large as the nucleus of the epithelial cells; but a definite nucleus has not been made out. Presently segmentation takes place, leading to the formation of small round bodies about 1 micron in diameter. These bodies are regarded as living organisms, and their gradual growth and final segmentation as a cycle of their life-history. At the period of segmentation and when most of the intracellular bodies have disappeared, small round or oval ring-like bodies appear in the nucleus. These increase in size,

¹ Zeitschr. f. Hygiene und Infektionskrankheiten. Bd. xxxviii, 1901, p. 212.

acquire a definite structure, and lead to degeneration of the nucleus. The intranuclear body is regarded as a further stage of development of the intracellular body, and as representing a second complete cycle of development, arising from the spore-like bodies produced by the segmentation of the intracellular body, which pass into the nucleus. The spores produced by segmentation are regarded as the true infecting material of variola. In vaccination of the rabbit and the calf, bodies similar to those met in the first cycle of the small-pox organism have been seen, but the intranuclear forms have not been found. Inoculation in the monkey, however, disclosed both the intracellular and intranuclear forms, whence it is thought extremely probable that in smallpox the complete development of the parasite through two cycles takes place, and that in vaccinia the primary cycle only occurs. The author of the paper states, however, that definite conclusions can only be reached by further study of vaccinia in animals subject to both vaccinia and variola. —Ed.]

Whereas cowpox is only transmissible by inoculation, the contagious principle of human smallpox is distributed by the air surrounding the patient and may, therefore, be inhaled by healthy persons and thus show its activity. A very brief presence in the sick-room is sufficient to produce the disease in any susceptible individual. This is probably possible already in the first days of the disease even before the skin shows any eruption, as well as in those rare cases in which no eruption occurs at all (*variola sine exanthemate*).

The contagious principle is besides contained also in the secretions of the mucous membranes and probably also in the other secretions. Above all, it is present in the contents of the vesicles and pustules and in the crust from the drying of these parts upon the skin as well as in the desquamated epidermis.

By these excretions and waste products of the patient and by the contaminated substances due to this cause (linens, clothes, utensils of the most various kinds, also books, newspapers, letters) the contagious principle may be indirectly transmitted and the disease thus propagated.

The contagious material dried and pulverized in this manner being carried by the air may distribute the disease to great distances.

Many years ago it was determined in London that in the neighborhood of smallpox hospitals which were established in the midst of populous portions of the city, in spite of measures for the strictest isolation, a disproportional large number of cases arose in the immediate neighborhood. These hospitals had to be removed on this account. Now several smallpox hospitals are erected upon ships which are on the Thames below London. Here also in the epidemic of 1892 to 1895, and in the one of 1902, it was shown that, in the direction of the prevalent winds, the population upon the shore exposed to the winds were markedly affected by smallpox. Thresh,¹ having made careful investigations in this respect, believes that these hospital ships may exert an influence by means of the current of air for about 2 miles.

[The probable part played by the house-fly in the dissemination of smallpox in the neighborhood of local epidemics in which strict quarantine has been maintained and with an intensity diminishing as the radius of the distance increases in the neighborhood

¹ British Medical Journal, February 15, 1902.

of smallpox hospitals and ship hospitals has not been sufficiently studied. The fact that in some instances the spread of the disease has been in the direction of the prevailing winds is of importance in this connection.—Ed.]

The contagious principle is *very resistant and tenacious* so that it adheres to fomites, to the walls of rooms, to carriages which have been used by the patients, etc., and thus for a long time may be the object of contagion.

When a susceptible person is exposed to the contagion, upon an average, twelve days pass before the appearance of the first morbid phenomena. During this *period of incubation*, which, according to the observations of Eichhorst,¹ perhaps under the modified influence of former vaccination and revaccination, was determined to be only nine days and eight to fourteen hours in 3 unquestionable cases, the affected person usually is quite well, but all varieties of a milder degree of illness may even occur during this period.

CLINICAL PICTURE

As a rule, the disease begins *very suddenly*, often with a decided chill, as the accompaniment of a rapidly rising temperature, frequently with *vomiting*, in small children as the equivalent of the chill, with convulsions. The symptoms which accompany every abnormal rise in temperature, general lassitude, pain in the head and limbs, insensibility and delirium, occur in smallpox with a special severity. This is especially true of pains in the lumbar region which in no other febrile disease attain such magnitude. In combination with the distribution of these pains anteriorly and in the inguinal region, they may resemble a spinal meningitis with irritation of the sensory nerve roots. That, in fact, the spinal nerve roots in question are the seat of a particularly severe, probably toxic, influence is shown by the *vasomotor symptoms*, which are especially common in this region and are more severe here than elsewhere. While under the influence of the fever, i. e., therefore probably due to the toxic action of the pathogenic agent upon the vasomotor apparatus, *the skin of the entire body*, particularly upon the trunk, shows a *decided uniform reddening* which occasionally resembles scarlatina, due to the dilatation of the smallest arteries; *the lower abdominal region*, in the triangular space bounded above by a line running across the umbilicus, the apex of which is formed by the closed thighs, the sides of the triangle being bounded by the inguinal regions, shows a still more *intense reddening*, in which not infrequently even vasomotor paralysis with destruction of the capillaries occurs, therefore leading to the formation of smaller and larger purpuric areas. Later a severe "hemorrhagic" form of smallpox will be described in which purpuric spots and larger hemorrhages appear over the entire body. The small cutaneous hemorrhages in the lower abdominal region must not be confused with these petechiae. They may occur in cases which show subsequently no especially severe course.

Occasionally markedly distributed erythematous patches appear in other portions of the body, for example in the axillary region. Eruptions resembling measles appear transitorily especially upon the extensor surfaces of the thigh.

¹ Deutsche med. Wochenschr., 1886, Nr. 3.

The patient who for any reason breathes with an open mouth, even in this first stage of the disease, *suffers pains in the throat, due to a dryness of the mucous membrane* of the isthmus of the fauces, with marked redness, appearing over night, which, on account of the very conspicuous febrile cutaneous erythema, may raise the suspicion of scarlatina.

These general phenomena of the INITIAL FEVER last in quite uniform severity, with the temperature often rising above 104° F., for two days, twice twenty-four hours, occasionally somewhat longer. Then, with the *remission of the fever*, a *general amelioration* of these constitutional symptoms occurs, whereas the change in the skin, the *cutaneous eruption*, which is characteristic of the disease, now begins to develop.

With this decline in the temperature accompanied by sweating, which resembles the condition in measles noted on the third day of the disease, the pains in the head and back and the constitutional symptoms ameliorate. With occasionally a somewhat diffused redness appearing on the face, sometimes copiously, at other times less so, now upon the *third day*, sharply circumscribed *red nodules* appear; and also upon areas of the forehead or hairy scalp, upon which no redness can be noted, there are occasionally small hard nodes which feel like shot beneath the skin. Simultaneously, upon the dorsal surface of the hand, upon the forearms, then also upon the neck and trunk, similar, often intensely reddened nodules are noted. If they are not isolated they are often arranged in circular order or they collect in groups in individual cases. The frequently bluish-red color of the developing smallpox papules may resemble the eruption of measles, this is especially the case in plethoric strong adults. But the maculo-papules of measles are not as hard as those of smallpox.

In the course of a few days these papules, which constantly increase in number, gradually develop upon the trunk and lower extremities and become larger, and by accumulating fluid under the epidermis form into *vesicles*. Simultaneously an inflammatory area (areola) develops around the individual nodules (*variola discreta*), whereas in those areas in which the eruption is closer together or where it coalesces as is frequently the case in the face (*variola confluens*), there is a more pronounced inflammatory reddening and swelling in the entire cutaneous area.

The developed vesicle, which from the sixth to the ninth day of the disease attains its acme, is flat, showing in its centre a *slight depression*, it is, as the condition is expressed, "umbilicated." The contents which are *serous* at first rapidly become turbid; they become more and more *purulent*, the vesicle becomes a *pustule*.

This transformation is designated as "maturation" of the eruption, by which process the central depression of the pustule is gradually forced up again. The beautiful illustration in Alibert's atlas shows this, illustrating the appearance of the face in this stage of the disease. Upon the hairy scalp and in the ears these efflorescences may also develop more or less plentifully.

As in the face, on account of a more plentiful or confluent eruption, the subcutaneous cellular tissue, especially of the eyelids, shows serous infiltration, this swells to a marked extent, as does also the skin of the head. The eyes may be completely closed by this swelling. Some conjunctivitis, even without

pustules developing in the conjunctiva, is frequently present as early as during the initial fever.

In the cornea of the eye, the pustules of smallpox do not develop as was formerly believed. The very frequent severe changes in the eye which were so common previously, by which many persons lost their sight, occur alone in the stage of pustulation of the disease, the cornea and the deeper portions of the eye are only secondarily affected.

Not only in the skin, but also in the *mucous membranes of the nose, mouth and pharyngeal cavity*, and in the upper portions of the *esophagus*, as well as in the *upper respiratory passages*, the eruption may develop and give rise to the most varied, occasionally very severe alterations. Especially may deglutition be difficult and painful and as a result of this the *profusely excreted saliva may constantly flow from the mouth*. In spite of the profuse secretion of saliva, the mucous membranes of the mouth and pharynx, and especially the upper surface of the tongue, may become dry and fissured, as the result of occlusion of the nose by the pustules developing upon the mucous membrane, causing an exclusive respiration by means of the mouth. This increases the difficulties of the patient, making deglutition at times impossible. Beneath the dried epithelium and in the small fissures, secondary infection may regularly occur, producing glossitis and giving rise to marked edematous swelling in the palate and at the entrance of the larynx. These may produce difficulties in respiration, and even death from asphyxia, if tracheotomy is not performed in proper time.

The more *minute pathologico-anatomical changes* in the development of the pustules, which have been especially studied by Weigert, consist in a necrotic swelling of the cells of the rete Malpighii with desquamation of the same. Between these areas which are thus changed, cell columns remain which show a greater resistance, so that the vesicle in smallpox and the pustule which forms with increasing leukocyte infiltration presents a *many-partitioned structure*. By the continuance of less altered cell-columns, the connection between the epidermis and the surface of the capillary body is retained, this causing the central umbilication. Small-celled infiltration may liquefy the capillary body to a considerable depth so that a part of it is also concerned in the process of maturation.

The development of the smallpox efflorescences to pustules, therefore its maturation, is due to the severity of the disease, which is again dependent upon the infection and upon individual conditions, requiring from nine to twelve days. Not all efflorescences develop to the same extent, even in the severest cases. There are always individual ones, especially upon the trunk and upon the extremities, which from the onset show a less marked development, never attaining a greater size than a small acne pustule, with a small, more punctiform crust than the fully developed ones and more rapidly drying.

There are some cases of smallpox in which the greater portion of the eruption, which even then is but slight in extent, shows this more abortive course. These are cases of very mild course due to a slight infection or lessened susceptibility, as occurs from a previous attack of smallpox or after vaccination. These mild cases in which occasionally the disease seems to have exhausted itself in the initial fever, has been designated as "*varioid*" or modified smallpox to distinguish them from "*variola vera*." As has already

been indicated, this is only a *milder form of the same disease*. A non-protected person coming in contact with such a mild case may contract the most severe form of the disease which may run a fatal course.

The pustules partly rupture, or they are caused to rupture by friction or pressure of the bedclothes covering them, and a part of the sero-purulent contents exudes and dries upon the surface. In the pustules which remain closed the *contents also gradually dry, whereas the surrounding redness and inflammation of the skin decreases*. Thus, crusts are formed which extend into the papillary layer.

Many deviations from the usual character and course of the smallpox exanthem have been described under special names. A mild form of smallpox has been described as *variola verrucosa or cornea*, in which, after a severe initial fever, and after the disappearance of all other phenomena, large, very unequal efflorescences appear which develop but slightly and therefore remain more papular, rapidly drying, without leaving scars. Therefore, an especially mild form of varioloid. In contrast to this, is a variety known as *variola corymbosa*, in which a grouping of the sparse efflorescence occurs, in which the individual pustules form in cluster-like groups which are not rarely symmetrical, attaining the size of a silver dollar or of a small plate, showing frequently an unfavorable course.

Upon the mucous membrane of the mouth and pharynx, in very obese patients, also in areas of the body in which the cutaneous surfaces are constantly in contact with each other, the covering of the pustule softens and ulcers form, which, upon the mucous membrane of the mouth and pharynx, resemble aphthous ulcers, but, provided no complications occur, heal more rapidly than the pustules upon the skin.

Upon the surface of skin as well as in the aural cavity and in other areas, under the influence of bacteria of all kinds, decomposition of the exuding and drying pus rapidly occurs, by which process offensive gas-producing decomposition products form which may render the air in the sick-room unendurable. *The smell which smallpox patients in this stage exude is a very peculiar, specific one.*

While the drying of the pustules occurs gradually (*stadium exsiccationis*), the *fever, which in all severe cases reappears with the beginning of the eruption, and rises step-like, declines slowly by lysis*. The drying of the eruption as well as the retardation of the fever varies greatly in duration in different patients, without even complications having appeared.

Beneath the crusts new skin formation occurs, so that when the former loosens and falls off, flat, somewhat depressed, usually round, scars remain, these are commonly uneven, due to small punctiform depressions, which in the first period and often for months, especially in the colder season, remain somewhat cyanotically reddened. Only very gradually do they become pale, in a brunette skin even paler than the surrounding healthy skin. In the region in which several pustules have coalesced, especially in the face and here particularly in the region of the alæ of the nose, there form, as the result of deep pustulation, scars which radiate, giving rise to deformities.

The severe focal inflammation of the skin and of the mucous membranes, in the course of which *secondary infections* are very apt to arise, thus producing complications of all kinds, such as erysipelas, lymphangitis, with secondary

enlargement of the lymph glands and abscess formation, inflammation of the subcutaneous cellular tissue as well as of the submucous connective tissue, but even occurring without such intercurrent conditions, frequently shows after complete recovery a tendency to many pathological changes such as acne, furunculosis and seborrhea. Alopecia arises after severe cases.

We must now after having described the changes in the skin which are the most conspicuous manifestations in smallpox, return to the constitutional symptoms of the disease. The improvement in the condition of the patient,

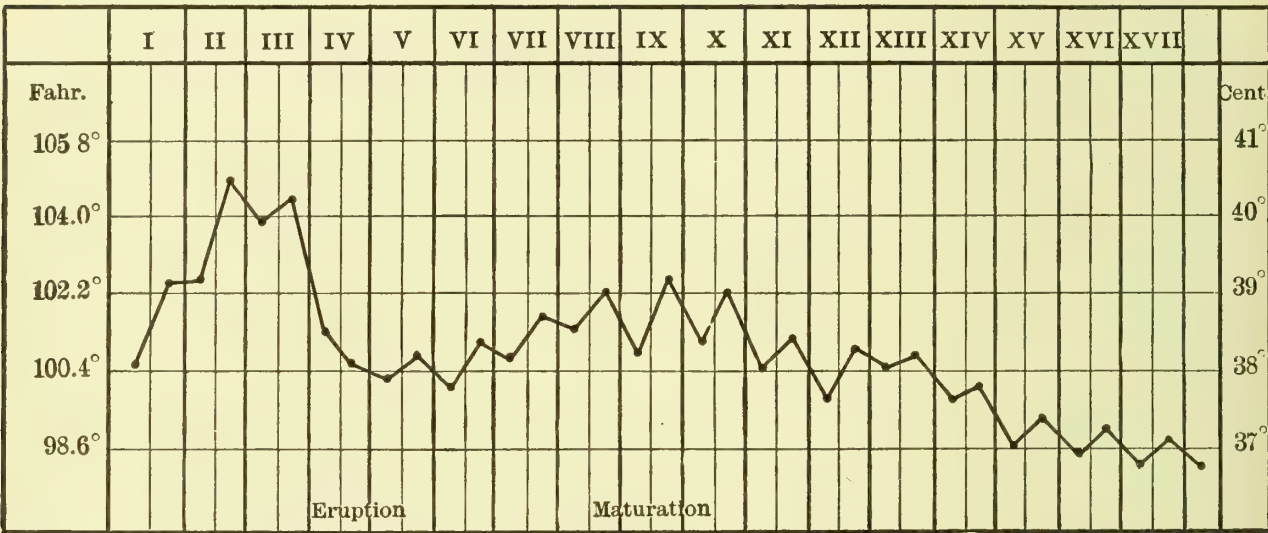


FIG. 31.—TEMPERATURE CURVE (VARIOLA DISCRETA). (After Curschmann.)
Medium severe case.

which occurs with the fall in the fever on the third day of the disease, in severe cases is of brief duration. With the development of a profuse, occasionally of a confluent, eruption which increases from day to day, the fever returns and now in the second week of the disease, the clinical picture may become a very severe one. Not only the irritation due to the inflamed skin, affecting numerous sensory nerves but the pains which occur in the fingers and palm of the hand, upon the soles of the feet and in the toes which are due to the pustules which develop under the thick unyielding epidermis, the immobility of the limbs which is the result of tension, the difficulties which are due to affections of the nose and mouth, but also the toxic effect of numerous pus foci, frequently give rise to the most *severe nervous disturbances*. Delirium, mania terminating in coma, delusion which may cause attempts at flight or develop suicidal tendency, occur frequently. Especially are alcoholics subject to these severe disturbances, in them a typical *delirium potatorum* may develop.

This by no means exhausts the phenomena on the part of the *nervous system* in the course of smallpox. Focal affections of the brain, of the spinal cord or in the peripheral nerves, whether due to the specific pathogenic agent of smallpox or to pyogenic organisms which have been added by the secondary infection, may produce the most varied phenomena, above all paralytic conditions, which may only appear after the disease has run its course.

As in every other severe febrile disease, so also in variola, *bronchitis* and *bronchopneumonia* may occur as complications, and this takes place all the

more readily the more the upper respiratory passages are implicated in the process. Frequently, in the course of severe variola, *pleurisy* occurs, more rarely lobar pneumonia.

It is quite obvious that in an affection with innumerable pus foci, the most varied *metastatic inflammations* may occur. Purulent arthritis, periostitis, general sepsis, with or without metastasis, may develop. From the oral cavity, or by metastasis, *parotitis* occurs, but this is a comparatively rare complication. More frequently is there *otitis media*. Phlebitis is not so rare. In very severe cases, in both sexes, gangrene of the external genitalia has been observed. Bedsores can only be prevented with the greatest difficulty.

The not infrequent inflammation of the testicles or ovaries probably results from the direct action of the causative agent of the disease.

In patients with high fever, *albuminuria* is frequent, which, however, disappears with the fever. Whether the *diazo-reaction* occurs is still undecided. Parenchymatous nephritis of a high degree develops but rarely, in sepsis occasionally purulent interstitial nephritis occurs.

The *spleen* shows no constant condition. Curschmann found the spleen markedly enlarged in variola vera, but no enlargement worth mentioning in varioloid. Decided enlargement does not occur in uncomplicated smallpox.

After having described the general course of the disease and the principal phenomena, it will be well to regard the *temperature curve* somewhat more in detail.

In the temperature chart above will be seen a case of smallpox terminating in recovery, and in this two principal divisions may be differentiated: 1. *The initial fever* that has terminated upon the third day or at least has declined considerably; and 2. *The fever which has gradually reappeared with the development of the exanthem and has fallen with the decline of the eruption.* This second febrile period, which is also designated *suppurative fever* [secondary fever], lasts from ten to fourteen days. Any decided complication which occurs in this stage will be expressed in the fever curve, which, as a rule, belonging to septic processes, causes an indefinite *prolongation* and gives rise to irregularities in the fever course.

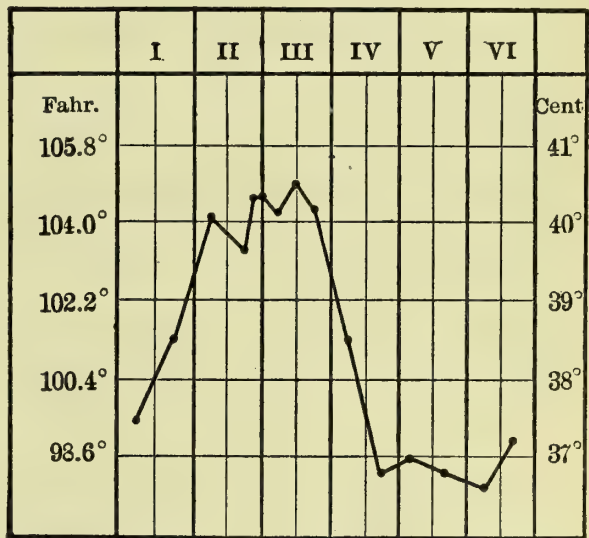


FIG. 32.—VARIOLOID. (After Wunderlich.)

A *milder course* of the affection, as in many cases of "varioid," is shown in the curve, in that the *second febrile period may be entirely absent* (Fig. 32). The specific changes in the skin are not severe and are too sparse to produce fever. Or this second febrile period is indicated by a milder rise of temperature of brief duration (Fig. 33).

Nevertheless, even in such cases, the initial fever may be high and may be accompanied by very severe general phenomena.

In such individuals that have not acquired any degree of immunity by a

previous attack of smallpox or by vaccination, smallpox just as all other infectious diseases, may show *varying grades of severity*. Accurate descriptions of the disease from previous times denote this clearly. Besides the individual varying susceptibility the specific cause of the disease, i. e., the exciting cause, according to quantity and quality plays a rôle.

I have previously indicated that an abortive form without the specific eruption occurs "*variola sine exanthemate*," which had already been described by Sydenham. Its occurrence with *the possibility of transference to others, giving rise to the ordinary form of smallpox*, has been determined with certainty by later observations.

The usual milder forms of the disease designated as *varioloid* occur in all possible grades, with but very few or numerous pustules which are, however, isolated (*variola discreta*). They may be very numerous and then, in keep-

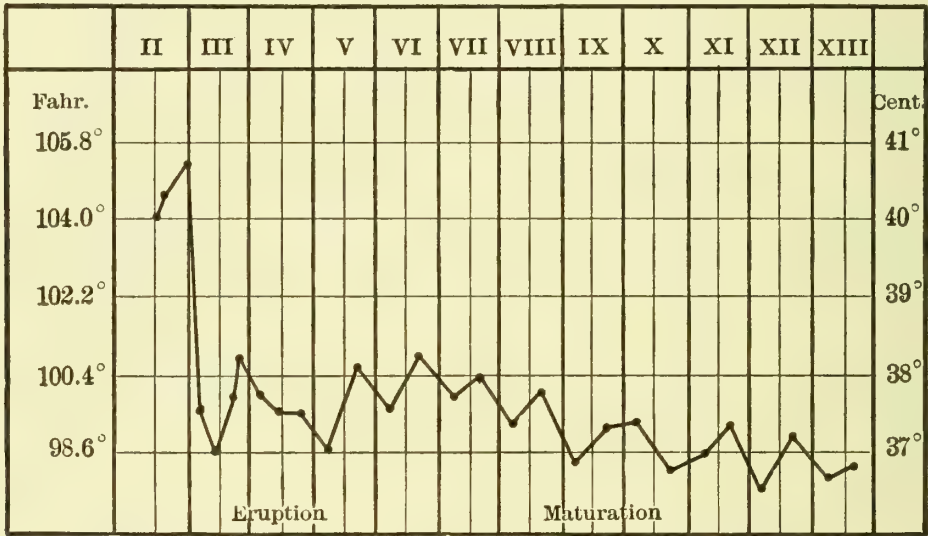


FIG. 33.—MILD CASE (VARIOLOID) FREIBURG CLINIC.

ing, a severe course of the affection occurs so that an imperceptible transition of this form to the severest *variola confluens* occurs.

Besides those already mentioned, there are also some *other forms* of variola, which regarding their occurrence, individual and external conditions, (chronic organic disease, general nutritive disturbances, alcoholism, method of living) play an important rôle, rather than a possible modification of the course of the disease. These are the *hemorrhagic forms* of variola in which either

1. *Very early*, even during the initial stage, or
 2. *Only during the period of eruption*, the *hemorrhagic diathesis* develops.
- In the first instance, with but slight fever, but with very weak, frequent pulse, the entire appearance of the patient being that of collapse, cutaneous and mucous membrane hemorrhages occur. Besides ecchymoses, there may also be small punctated and vesicular hemorrhages in the skin. The facial expression of the patient is then especially terrible, if, besides the cyanotic pallor, there is a wasted condition of the face and the eyes are injected with conjunctival hemorrhages. This form which corresponds to the hemorrhagic forms of scarlatina and measles is called "*purpura variolosa*." The patient usually succumbs within the first few days of the disease. Pregnant women abort, as occurs in all severe forms of variola.

In the second form, the course of the eruption takes place in the usual manner, but the vesicles are filled with *hemorrhagic contents* and when maturation occurs the efflorescences assume a black color, hence the origin of the name "*black smallpox*" which in Germany is frequently applied to smallpox of any variety. Besides the specific eruption there may occur in the skin and subcutaneous cellular tissue as well as in and under the mucous membranes, large effusions of blood and there may be hemorrhages from any of the outlets of the body. This second form is differentiated from the first and called "*variola pustulosa hemorrhagica*." Not all the cases of this variety in which the eruption becomes hemorrhagic, take an unfavorable course. In some of these cases, as observed by Scheby-Buch and W. Osler and in milder cases of this kind there is a rapid drying of the pustules.

A special course is taken by smallpox if contagion does not occur in the usual manner, through absorption by way of the respiratory organs, but when *the contagion is introduced into the skin through a small wound*, when it is "*inoculated*."

At the end of the eighteenth century and at the beginning of the nineteenth until vaccination became general, there was a frequent opportunity of observing the course of *artificially inoculated smallpox*, called "*variolization*."

In the Orient, the artificial inoculation of smallpox had been practised for a long time as it was observed that smallpox attacked man but once, as a rule, and that the *artificially inoculated disease ran a milder course* than that brought about by the usual contagion. At the beginning of the eighteenth century reports had come to England from Turkey, but only the example of Lady Mary Wortley Montagu, the wife of the English Ambassador at Constantinople, who, surprised by the favorable results noted in the milder course of the disease, of which she had heard while in Constantinople, had her own son inoculated and having returned to England had the same process carried out for her daughter (1721), gave an impetus to the method and it was first adopted in England and from there spread over entire Europe. In 1746 there was founded in London a "smallpox and inoculation hospital" which remained in existence until 1822. Only in 1840 was the method finally abandoned and forbidden by law. The reason for this was the *danger of distribution of smallpox by such inoculated cases*, and then, above all, because of the substitution of Jenner's method of vaccination of cowpox, which had been successfully practised, and had been found to be just as effective, and if repeated sufficiently often, even more active in its protection against smallpox, and perfectly harmless if the necessary precautions were observed.

What is the course of smallpox in artificial inoculation of smallpox in *variolization*? At the point of inoculation, on the third day, a small nodule develops, which upon the fourth day becomes an umbilicated vesicle, on the sixth day the axillary glands become enlarged and are painful, upon the seventh day, or more frequently upon the eighth, fever with its usual symptoms occurs, occasionally even with vomiting. This is followed after a few days by the *appearance of the general eruption*.

By this direct transference of the toxin into the fluids of the skin, the *period of incubation is shortened several days, up to five days*; after the development of a *local* inflammatory irritation at the point of infection there follows, after a preceding initial fever, the general eruption which, as a rule, runs a course resembling modified mild smallpox.

The *mortality* from smallpox varies greatly according to whether the

disease occurs in unprotected persons or in those who have passed through an attack of smallpox or in those that are partly protected by vaccination and revaccination. *Children in the first year of life that have not been vaccinated invariably succumb to the disease.* In “variola confluens” even to-day the mortality may amount to 50 per cent. On account of insufficient vaccination only partly protecting the individual, according to the grade of protection still present, the mortality may vary from 2 per cent. to 25 per cent. Up to a certain degree the subsequent protective action of vaccination may be calculated:

1. According to the time which has passed following successful vaccination. Experience teaches that the protective power diminishes after about ten years.

2. According to the number of well-marked vaccination scars present.

I shall quote here the important compilation of J. F. Marson¹ regarding these conditions, of cases from the London Smallpox Hospital from the years 1836 to 1855; of 2,654 *non-vaccinated* persons who were admitted during the years 1836 to 1851 there was a mortality of 37 per cent. Of 4,896 vaccinated persons (or supposed to be vaccinated) during the years from 1836 to 1855: 8.2 per cent. died, among them with one scar, 2,001 cases with 9.3 per cent. mortality; with two scars, 1,446 cases with 6.1 per cent. mortality; with three scars, 518 cases with 3.0 per cent. mortality; four or more scars, 544 cases with 0.9 per cent. mortality; without scars but supposedly vaccinated, 370 cases with 27 per cent. mortality; supposed to be vaccinated, but no sign of scar, 17 cases, with 17 per cent. mortality.

Death occurs either through exhaustion of the nervous system after severe delirium and coma, occasionally from excessive rise in temperature, often hypostatic pneumonia with cardiac asthenia, or by septic complications and various sequelæ. More than one-half of the fatal cases succumb in the second week of the disease. Sydenham regarded the eleventh day of the disease, the ninth after the appearance of the eruption, as a dangerous one. According to compilation from the London Smallpox Hospital, this day of the disease proves to be especially fatal, in fact the period between the tenth and fourteenth days. This would favor the fact that septic influences are especially prominent as a cause of the fatal termination. From the true toxemia of smallpox, only cases of purpura variolosa succumb.

The important and specific *pathologico-anatomical changes* are noted in the skin, and of these I have already mentioned the most important points. Of the mucous membranes, only those of the exits of the body are primarily attacked. In the mucous membranes of the internal parts of the body, no analogous parts are found which resemble the eruption. In the intestinal mucous membrane, the lymphatic apparatus may be somewhat enlarged. Miliary necroses, analogous to those which give rise to the focal reactive cutaneous inflammations, may be found in the parenchyma of the internal organs, such as the liver, the kidneys, the brain and spinal cord, as well as arising from the vasa vasorum in the walls of the vessels, and from the branches of the coronary arteries attacking the heart muscle. These have been

¹ J. Russell Reynolds' System of Medicine. London, 1866, v. i, p. 473.

determined upon several occasions, but it will be difficult to decide how much of this is due to secondary septic infection.

The grosser changes in the lungs are the same as those noted from other infectious diseases.

DIAGNOSIS

The diagnosis of smallpox may be very easy if the eruption has already developed. On the other hand, in the case of modified smallpox, of so-called varioloid, it may be exceedingly difficult to decide. And yet much may depend upon this decision, especially if unprotected, or insufficiently protected, persons, especially small children that have not been vaccinated, come in contact with the patient. In countries in which, such as in Germany, the vaccination laws are strictly carried out among all inhabitants, in which the masses of the inhabitants are protected by vaccination, and mostly by revaccination, such mild cases, of doubtful smallpox, even as regards the eruption, occur quite frequently. Two rules must be followed in such cases: 1. To think of smallpox, and 2. Not only to make the diagnosis upon the basis of an eruption resembling smallpox, but to carefully take into consideration the course of the affection and to investigate the condition of the patient minutely, endeavors being made to determine the possibility of a smallpox infection, accordingly in what section of the country the patient has been living immediately previous to his illness.

As we have seen, the eruption of the exanthem is always preceded by an *initial fever lasting two days*, which is always accompanied by at least some mild general symptoms, frequently by well-developed *pains in the small of the back*. Such symptoms must always appear as very suspicious if the patient has come from a district or a region in which smallpox is present.

Regarding the *eruption*, according to the stage of the disease, confusion may occur:

1. So long as only red maculo-papules occur in the face and upon the dorsum of the hand, with *measles*. The efflorescence of measles may, upon its first appearance, in isolated portions of the face, upon the neck, upon the hands and forearms, in young adults with a tough skin rich in blood vessels, show the greatest similarity to the development of the eruption of smallpox. In fact, according to the reports of physicians in smallpox hospitals, such confusion frequently occurs. As house physician at the German Hospital in London, I made this mistake myself and sent a patient with a conspicuously profuse and very prominent eruption of measles to the smallpox hospital, whence he was soon sent away with a diagnosis of measles. After twenty-four hours there can no longer be a doubt as to the true diagnosis. Such an error may be prevented if it is remembered that the eruption of measles occurs upon the fourth day, and not, like smallpox, on the third day after the onset of the initial fever, that in measles usually marked catarrhal phenomena on the part of the nasal and conjunctival mucous membranes are present, that upon the mucous membrane of the oral cavity Koplik's spots are present. A very important differential sign is shown by the urine in measles; as a rule, at the time of the appearance of the exanthem, a very marked *diazo-reaction* occurs and is more noticeable, perhaps, than in any other disease.

Severe pains in the loins, a coarse appearance of the eruption, the feeling of small hard nodules, resembling small shot, under the skin of the forehead, which is not yet reddened, favor the diagnosis of *smallpox*.

If in such doubtful cases the history regarding the onset of the fever, etc., cannot be determined with certainty, the case may be doubtful up to the point of further development of the eruption. The patient must then be carefully isolated. On the following day the eruption will show that the nodules present the previous day have not enlarged but that their number has greatly increased, that confluence has partly occurred in groups in which the more intensely reddened follicles of the skin are more prominent, that the eruption and the entire, now swollen, face of the patient is of a more bluish-red color, that more fever is present, thus plainly designating the eruption of measles. But if the individual nodules have enlarged so that in some the epidermis has been raised, forming a vesicle, whereas new nodules of the consistence of the first have appeared, the patient having remained free of fever or showing but slight subfebrile temperature, then it is certain that we are not dealing with measles but smallpox.

2. If a case shows vesicles, partly with clear and partly with already purulent turbid contents, there must be considered, especially if the patient is a child, above all, an affection perhaps distantly related to variola, namely *varicella*, water-pox, wind-pox, or chicken-pox.

Largely by the earliest authorities, as also by Hebra, varicella was looked upon as the mildest form of smallpox. That this is not true, but that it is an affection *sui generis*, is now determined with certainty. For:

1. Recovery from varicella does not protect from smallpox. Marson reports that patients who are brought into the London Smallpox Hospital with varicella have there contracted smallpox, and relates the case of a child that having recovered from smallpox, and been discharged from the smallpox hospital, was, after a brief period, brought back attacked by varicella;

2. Children who have passed through an attack of varicella are susceptible to vaccination;

3. The initial fever lasting two days is absent in varicella. The disease begins at once with the eruption, which, therefore, appears inside of the first twenty-four hours of the affection;

4. The period of incubation of varicella is a different one, it is from thirteen to seventeen days;

5. The individual efflorescences take a much more rapid course in their development than in any form of smallpox, even on the third day of the disease vesicles are found with turbid contents, and upon the fourth day the process of drying begins;

6. The vesicles and pustules of varicella are globular, are not umbilicated and do not consist of compartments. The inflammatory areola at their base is but slight, the cutis showing no inflammatory infiltration.

Of other diseases which show a vesicular or pustular eruption, there must be mentioned syphilis, erythema exsudativum multiforme, and pemphigus.

In *syphilis with a vesicular or pustular eruption* there is not infrequently a great similarity to the individual efflorescence in smallpox, and if such an eruption occurs acutely in syphilis, in the so-called eruptive stage, being

accompanied by constitutional symptoms (fever, great lassitude, severe headache) the entire clinical picture may show a certain similarity to smallpox; however, close investigation of the patient will rapidly decide whether we are dealing with syphilis or with smallpox or with both simultaneously, which, naturally, occurs.

In favor of a *syphilitic eruption* are, the cachectic appearance of the patient besides a *moderate enlargement of the spleen*, indolent *lymph-gland enlargements* in the *inguinal, cervical* and *cubital regions*, if, besides well-developed vesicles and pustules, there are older forms with crust formations, or if, after desquamated crusts, flat infiltrations are found in the skin. Usually with an eruption of this kind, specific changes—papules or ulcers—in the throat are simultaneously present. The fever which accompanies an eruption of this kind in syphilis is as a rule markedly remittent, occasionally even quite intermittent, accompanied by chills. Naturally the *history* in regard to the duration of the fever, the appearance of the eruption, the preceding phenomena which are in connection with syphilitic infection are of great importance.

In *erythema exsudativum multiforme*, which may appear as a “dermatitis herpetiformis,” in pregnant women under the form “herpes gestationis” with numerous and repeated eruptions of a vesicular or pustular character in which the efflorescences may closely resemble smallpox, we are dealing occasionally with a very acutely arising affection or an acute relapse, in which the entire clinical picture may be suspicious of smallpox, especially if smallpox is present in the vicinity in which such a case occurs. Careful questioning regarding the previous course, the simultaneous presence of partly larger flat, not coarse, mostly light red, erythematous papules, besides vesicles and pustules which are occasionally arranged in circles (herpes iris), the proof of somewhat enlarged lymph glands at various portions of the body, as well as enlargement of the spleen with moderate fever, permit us, even if not at once, however, in the course of one or two days, to decide the case.

Pemphigus vesicles, only if they are quite small, show a similarity with the vesicles of smallpox; they differ, however, by their globular shape, their rapid appearance, the absence of a distinct inflammatory infiltration at their base, and the paroxysmal appearance.

Very probably all of these diseases, which run a course with the development of vesicular and pustular eruptions, are due to some *form of sepsis* caused by a causative agent not yet positively determined. The accurately known forms of sepsis also, such as ulcerative endocarditis and the so-called cryptogenetic sepsis which run their course with severe constitutional symptoms and high fever, may show an eruption resembling smallpox, and which, if they resemble acne, have a great similarity to the efflorescences of modified smallpox. But the paroxysmal appearance interrupted by longer pauses, and the other constitutional phenomena are sufficient to prevent confusion with smallpox. Osler¹ mentions a case of glanders which was erroneously taken for smallpox. Especially in districts and in times in which smallpox occurs frequently, such confusion may be avoided by a careful and accurate investiga-

¹ W. Osler, The Principles and Practice of Medicine, 3d ed. Edinburgh and London, 1898, p. 67.

tion, and this cannot be emphasized sufficiently, and also by an exact determination of the history.

To have properly and early diagnosticated an actual case of smallpox, even of the mildest grade, is of extraordinary importance for the reason that in districts and countries that are insufficiently protected by vaccination the welfare of hundreds, even of thousands may depend upon this. To make this clear I shall communicate an occurrence from North America, from Prof. Osler's description.¹ In the city of Montreal in Canada, during the period from 1875 to 1885, no cases of smallpox had occurred and protection by vaccination had been neglected. On February 28, 1885, a conductor upon the railroad, who came from Chicago where smallpox was present, was admitted to the Hôtel Dieu. He was not isolated as varicella was diagnosticated. On the 1st of April a servant girl in the hospital died of smallpox and then, as Osler says, "with a negligence absolutely criminal" the authorities of the hospital dismissed all patients showing no symptoms of contagion who were able to go home. This was the origin of a rapidly developing epidemic, in which, in the city, 3,164 persons, among them 2,717 children under ten years of age, died.

Especial difficulties are occasionally encountered in *purpura variolosa*; this can only be diagnosticated with certainty if contagion with smallpox can be assumed as likely, therefore, if smallpox is present in the locality or if the possibility of contagion anywhere else may be assumed. The hemorrhagic forms of scarlatina, of typhus fever, and the much rarer form of measles may show a similar clinical picture.

PROGNOSIS

The prognosis of smallpox has been entirely changed since Edward Jenner's discovery of vaccination, as now in all civilized countries, at least the greater part of the population is protected by vaccination, which is enforced by law or AT LEAST SHOULD BE. Therefore, in such countries in which a smallpox epidemic appears, the number of mild cases modified by vaccination shows a much greater percentage than in former times, and, in populations that have no protection by vaccination, previous epidemics of smallpox have partly rendered the people immune. I refer to the previous statistics regarding mortality which have been mentioned upon pp. 421 *et seq.*

In the individual case the following points are important in the prognosis:

1. The profuseness of the eruption which was already emphasized by Sydenham, the more copious the confluence of the eruption in the face, the more the hands are covered, the slighter the hope of recovery;
2. The severity of the cerebral symptoms; marked delirium, great restlessness are of unfavorable prognosis;
3. Marked implication of the upper respiratory passages or complication with bronchopneumonia or pleurisy are unfavorable;
4. In women, the prognosis is rendered unfavorable by pregnancy, as frequently, although by no means always, abortion or miscarriage occurs;

¹ *Loc. cit.*, p. 57.

5. Of the hemorrhagic forms, *purpura variolosa*, as already mentioned is also fatal. *Variolosa pustulosa hemorrhagica* is unfavorable in the majority of cases;

6. The severity of the symptoms of the initial stage, especially the height of the fever, only allows the conclusion of a further severe course. Much depends upon the question as to whether the patient has been vaccinated, and whether the protection is still active to a certain extent. In such a case, even after a severe initial stage, a modified form of the eruption may appear with either an afebrile period or a stage of slight fever accompanying the stages of eruption and exsiccation.

An initial hemorrhagic eruption denotes a severe course.

7. Even in the modified forms the age of the patient, his constitution, the presence of organic changes are of great influence upon the prognosis; the prognosis is exceedingly unfavorable in alcoholics and in those affected by inanition and unfavorable external circumstances.

PROPHYLAXIS

After what has been said regarding the danger of smallpox, it need scarcely be emphasized how very important an effective prophylaxis is in this affection. By far the most important agent which affects man, as has already been mentioned, is protection by vaccination, which was scientifically established by Edward Jenner and has since then been more completely worked out.

How extraordinarily great the influence of protective vaccination, enforced by law, in the appearance and course of smallpox, may be best seen from the statistical compilations in the previously mentioned book of Kussmaul, and in the memorial of the Board of Health of the German Empire as also in many other writings. I will only emphasize one point, that under the influence of our German laws from April 8, 1874, the mortality from smallpox among the civil population of the German Empire, between the years of 1875 and 1894 inclusive, in no year was greater than 3.6 to the 100,000, in individual years amounting to only 0.1, and in the military population, only in fact in the year 1885-86, 0.3, in the other years amounting to 0. Any one who casts a glance over the tables in the Board of Health Department of the Empire, and notes the experiences which were gathered during the war of 1870 and 1871 in the German army, in comparison with the French army, and is not convinced of the value of vaccination, is insusceptible to the force of logic.

Every physician must become minutely acquainted with these experiences not alone to act properly in the given case but to be able to defend vaccination from the foolish objections which frequently enough are made against it.

Experience has taught that vaccination is only protective for a number of years, hence the necessity for revaccination which, according to our laws in Germany, must take place in the twelfth year of life.

If any one is exposed to the contagion of smallpox and has not been successfully vaccinated a short time previously he must at once be revaccinated. This rule must be adhered to in all persons who in any way come in contact with a patient, with his linen, clothes, etc.

Here an important and interesting question arises, namely: Has vaccination with cowpox still an influence if it occurs after contagion with smallpox, but before the period of incubation has run its course? According to Marson, this is only the case if the vaccination has occurred so early that the areola of the vaccine pustule becomes fully developed before the symptoms of smallpox have appeared. In primary vaccination this is the case upon the seventh or eighth day after vaccination; in revaccination the areola is formed two or three days sooner. According to this, successful revaccination of one already vaccinated in youth would be effective two days later than in a primary vaccination. If smallpox occurs during the course of the development of the vaccine pustule, the later process is destroyed.

The patient should be carefully isolated, preferably in a hospital if there is one in the city. In larger cities, as here in Freiburg, smallpox patients are received in a special hospital.

In preparing the sick-room for the smallpox patient, great care must be exercised, as the contagious principle adheres very tenaciously to all possible substances. Hence limitation in furnishing the room, curtains, carpets, and all materials should be removed to the utmost and all such substances should be thoroughly disinfected.

This leads us to the discussion of

TREATMENT

In no disease does nursing of the patient require so much care as in this malady, for in no other is there so great danger of new affections, secondary infections being added to the disease. Even at the onset, owing to the severity of the affection or to the individual predisposition of the patient, the sensorium is disturbed, which condition is even increased in those cases in which suppurative fever appears, on account of the severity of the cutaneous involvement. In this stage there are numerous areas in the entire body, and in the mucous membranes of the nose, oral and pharyngeal cavities, from which, later, infections with other pathogenic agents especially those belonging to sepsis, occur. Above all, the most scrupulous cleanliness of the patient and his surroundings is necessary. In the stage of maturation of the pustules, the body and bed linen of the patient is soiled by the exuding contents of the pustules and for this reason it must be frequently renewed. The secretions from the mucous membrane of the nose and pharynx, as well as the profusely flowing saliva, in so far as they cannot be caught in suitable vessels, must be removed by cloths which are at once destroyed by fire. Everything that is washable is to be soaked in a lysol solution at once before it is thrown into the wash. All dejecta of the patient must also be disinfected.

As in every other febrile disease, the patient should be kept cool, nothing is more sure to increase the difficulty of the patients, the tension, the itching, the pain in the cutaneous inflammations, than warmth caused by heavy coverings and by warm air of the room. In early times the opposite was supposed to be necessary. Starting from the thought that the *materia peccans* was excreted from the body by the eruption and that the eruption was, therefore, an expression of the endeavor of the organism to produce cure, the attempt was made to drive out this by heat. As in other eruptive diseases nothing was more feared than the "driving in" of the eruption. John of

Gaddesden, the court physician of King Edward II, of England, who lived in the fourteenth century had his patients, among whom was also a son of the King, surrounded by red hangings, the room and the bed, the bed and body linen had to be of a red color, the entrance of air was carefully excluded.

A grain of truth may be contained in the view that the organism endeavors to rid itself of the toxic products of the disease which have entered by the circulation, but nowadays we know that the organism in itself is able to bring this about very much more readily and more completely under favorable circumstances regarding its functions (nutrition, ventilation, excretion, etc.). We know that a patient with fever is more comfortable in cool air than in warm air, that the cardiac activity and the respiration is slower and more productive than in the cases in which the cardiac activity is increased and the blood vessels are dilated by the action of the cause of the fever, without the hindrance of giving off heat caused by the high temperature of the surrounding air and the warm bed clothing. We also know that the fever patient requires more oxygen and that, therefore, the rapid change of the surrounding air is necessary and that more carbonic acid is given off and in the case of a smallpox patient after maturation and drying have begun also other deleteriously acting gases are given off.

Innumerable patients owe it to Sydenham that these tortures are spared them, many certainly owe him their lives; he courageously battled with preconceived opinions, firmly convinced that his process would carry off victory even if he did not live to see it. In ancient times, in the ninth century, Rhazes, in an epidemic of smallpox, advised keeping the patient cool previous to the appearance of the eruption; only after the eruption had appeared was the opposite treatment considered necessary.

A sensible general treatment similar to that advised by Sydenham was probably the reason of the success of two English physicians, the brothers Sutton, who, about the middle of the eighteenth century, enjoyed a great reputation as inoculators, because of the mild course of the disease in those inoculated by them. During the day they subjected their patients to cool air and at night had them sleep in large, well-ventilated rooms; they administered mild laxatives and limited the intake of nourishment.

During the initial fever the patients should be treated as in any other affection with high temperature, such as in enteric fever, scarlet fever or pneumonia; such patients with high temperatures have repeated cool baths administered, especially do the baths display their activity in opposing the febrile and toxic effects and insomnia. Under some circumstances baths of a higher temperature may be employed (86° to 90° F.), for ten to fifteen minutes water of a cooler temperature being poured upon those parts that are out of the water, thus upon the chest and back. Leiter's cooling apparatus may be applied to the head if cold is agreeable to the patient and diminishes his headache.

For the *vomiting* at the onset of the disease, carbonated drinks or effervescent powders are given; a plentiful administration of water is only useful in this and in the later stages of the disease.

Severe pains in the back may require the administration of salicylates or aspirin, phenacetin or other antineuralgic remedies, if these remedies are unsuccessful, morphia is to be used subcutaneously.

Nourishment must be fluid during the initial fever, especially because the patient will not take solid food in the stage of eruption and, further on, because of the involvement of the mouth and pharynx; deglutition may even be difficult or almost impossible with fluid food. In mild cases with but little eruption, and absence of suppuration fever, patients who desire it may have solid food.

Mouth washes of a warm physiologic salt solution or a solution of sodium bicarbonate or borax in tepid water should be used several times daily after administration of nourishment, in cases in which eruptions occur upon the mucous membranes of the mouth and pharynx. In severe cases the nurse, in so far as possible, must cleanse the teeth and mouth by cloths soaked in water. It is especially important that the nose be kept free by cleansing with a boric acid salve, boric acid in lanolin and vaselin being used to prevent crusting.

From the onset a laxative should be given to empty the intestinal canal, if necessary castor oil or compound infusion of senna, or any laxative powder can be administered; calomel should only be used at the onset, but by no means after the eruption has begun to appear in the mouth, on account of the danger of stomatitis.

From the diarrhea which is present in some cases, opium or bismuth subnitrate with or without opium, or, in the same manner, some of the newer tannin preparations, may be employed.

With the appearance of the eruption, the question must be frequently decided whether it is necessary to cut off the hair or not. In men this question can be settled without difficulty, but in girls and women we should only insist if at the onset a severe eruption, a variola confluens, is to be expected, if, in the stage of maturation, when the pustules begin to break down, the stickiness of the hair gives rise to great annoyance for patients and for nurses.

One of the chief questions in the treatment of smallpox, and with which physicians have concerned themselves in all times and even in our own time is this: What may be done to prevent the deep and numerous scars in the face, which occur in a profuse eruption, especially in variola confluens, and which distort the features? How can the cutaneous inflammation be controlled, and the formation of pus be prevented from entering the capillary bodies of the skin? The most varied modes of treatment and innumerable remedies have been devised for this purpose without much having been achieved by any of them. The chief indication consists in preventing the inflammation from spreading, by preventing irritation in which the local smallpox process must occur. Keeping the patient cool is primarily indicated, also the use of cold to a moderate extent, by means of frequently changing cold applications upon the face. These applications must be used with the greatest care and caution so as not to mechanically irritate while being applied and removed. They are grateful to most patients, and the majority of those who have had experience in the treatment of smallpox advise them. If it is desired, in an advanced stage of maturation, to dissolve an antiseptic in water, one must be chosen that will not irritate the skin; a weak boric acid solution will be best for this purpose.

In case of restless, resisting patients we must content ourselves with applying pure olive oil over the inflamed skin, producing a thin protective covering.

By some *ichthyol* in the form of a salve is warmly advised, for the sense of smell, as a result of an affection of the nasal mucous membrane, in some cases, is markedly diminished and the disagreeable odor of *ichthyol* need not be considered.

An irritation which must be considered in such a severe inflamed condition of the face is brought about by light. The experiences must have been quite certain which at various times gave rise to the advice to exclude all possible light and keep the patient in a darkened room. If the success of the exclusion of light is really so great as has been mentioned at various times the disadvantages of keeping the patient in the dark will be equalized. It has been thought that the withholding of the chemically-acting rays of light is necessary, this led to the fact that smallpox patients were kept in rooms with exclusive red light, therefore illuminated in the same manner as a photographic dark room, thus old John of Gaddesden, with his red color of the bed and coverings, has lately become prominent again. Whereas from several points, especially also from Copenhagen (Finsen), favorable reports have been communicated, on the other hand, systematic trials of this treatment in Lyon, instituted by Courmont, did not show a favorable result. It was also shown that the red light not only excited the patient but also the nurses to a high degree. This by no means decides the question regarding the "therapy of light" and it is quite possible that careful researches which are being carried out in the Finsen Institute in Copenhagen may clear up this question. In carrying out this principle, of keeping light from the skin of the face, this may be done by application and by the arrangement in the room; regarding the position of the bed, etc., this may be considered in a corresponding manner.

[Nils Finsen claims that unless an epidemic of smallpox is of an exceptionally severe character, the death-rate may be reduced 50 per cent. by the employment of the red-light treatment first advocated by him ten years ago. If, however, suppuration has begun, or is on the point of beginning, the red-light treatment will not control it. J. F. Schamberg does not believe in the efficacy of the red-light treatment of smallpox, and reports two cases of confluent variola in unvaccinated young men in which this treatment was employed after the third day of the eruption. One of these patients died and the other recovered with the most disfiguring scars. Finsen, in a second paper, calls attention to the unfairness of Schamberg's test, pointing out the fact that the two patients were unvaccinated, delirious men, with confluent smallpox, and were not subjected to the light treatment until the third day of eruption or about the seventh day of the attack.—Ed.]

The frequent discomforts which many patients have regarding the hands and especially the fingers, from the pustules which form there, are ameliorated by moist coverings and luke-warm hand baths from time to time.

When the pustules begin to "flow," by the careful powdering with salicylic powder at various portions of the face, and in other places by the application of a zinc guttapercha plaster, which is sufficiently often renewed, much may be done to ameliorate the condition of the patient and prevent the thick, sticky crust-formation. In confluent smallpox upon the body, and especially in open cutaneous pus areas which may form by the rubbing off or tearing off of the crusts, the permanent warm bath is as grateful to a smallpox patient as

it is for patients with burns or with other severe ulcerating cutaneous affections.

At various periods of the disease special care must be employed in keeping the eyes clean; if they are tightly closed by the swelling of the entire face or by pustules upon the lids, the accumulation of secretion upon the conjunctival sac may perhaps give rise to a severe conjunctivitis, which increases, producing marked disturbances in the cornea. The eyes should, therefore, be washed several times daily with a luke-warm boric acid solution, also compresses soaked with the boric acid solution may be applied from time to time. Processes which invade the eyes more deeply require treatment by a specialist.

After the pustules have dried completely and begun to loosen, frequent luke-warm baths are given to assist in their desquamation and increase normal healing processes in the skin; naturally, in this the greatest care on the part of the nurses is necessary; small open areas which remain after opening of the pus must be treated carefully and covered with a zinc guttapercha plaster.

In the initial stage as well as at the height of the development of the pustules, severe nervous phenomena may arise suddenly; the nurses should be instructed regarding the occurrence of severe nervous disturbances, such as delirium, mania, etc., so that the patient is constantly watched. Under such circumstances it is well to give a patient a luke-warm bath (86° F. to 90° F.) or a cool bath (77° F. to 80° F.), or there may be an administration of drugs, such as opium, codein, morphin or chloral hydrate, and if there is difficulty of deglutition these drugs may be given by rectum. Great care is necessary in hypodermic medication as the point of injection may readily become infected and thus become a pus focus.

Cardiac asthenia which is often threatening in the stage of maturation may require the use of remedies such as camphor. Alcohol is to be given to patients that are bathed, before and after the bath; the action of alcoholic drinks upon the pulse and upon the cerebral activity must be noted. In cases in which there is difficulty in deglutition physiological salt solution is to be given by rectum so that there is a sufficient absorption of water. If necessary, alcohol may be added to it.

Complications which occur during the course of smallpox or later on must be treated according to indications. Edema of the glottis may require tracheotomy. A large pleural exudate may require aspiration, and empyema, thoracotomy. Abscesses and phlegmons must be opened and drained. Endeavor should be made to prevent bedsores by scrupulous cleanliness and placing the patient on a water bed.

Sequels, especially those on the part of the nervous system, may require special treatment, such as electricity, massage and bath cures. Convalescence after severe smallpox may require residence for a long time in the country, under some circumstances a milk cure.

We are almost powerless in the *hemorrhagic forms of smallpox*. After the partly favorable results which have been attained by the use of gelatin in other severe hemorrhages, this treatment might be used in such cases, but naturally not in the form of a subcutaneous injection, but per os or per rectum.

Plentiful administration of nourishment, alcohol, decoctions of quinin, with sulphuric acid and camphor, are to be tried but they have generally proved to be useless in purpura variolosa.

After the experience of the last few years in the various infectious diseases, especially in diphtheria, with "serum treatment," this might be thought of in the case of smallpox. Experiments in this direction, however, have not extended beyond the first stages. The blood serum of inoculated calves contains immunizing properties, according to Bécélère, Chambon and Ménard.

I need scarcely describe the difference between the serum treatment of smallpox and cowpox vaccination. In the former case, the amelioration of the action of the causative agent of the disease, after the affection has appeared, or after the stage of incubation, by the antibodies in the serum inoculation would be meant. In the latter case we are dealing with the immunization of a healthy person, or one already affected by smallpox, by a similar infectious disease. In this case the antibodies which are necessary for immunization are formed in the body of the patient; in serum treatment the antibodies which are produced in the body of the animal previously treated are introduced into the patient in a finished condition.

Without question, an active serum treatment in severe smallpox, if used as early as possible, would be a great gain. If everywhere the experiences regarding the immunizing property of vaccination and revaccination, i. e., therefore, a high protection against smallpox, which have accumulated in thousands of instances should be utilized, the serum treatment would soon be superfluous. For it would be possible to exterminate smallpox altogether. I say possible, even although in smallpox with its resisting causative agent which is transmitted to the air the hopes are less than, for instance, in the case of bubonic plague which is especially due to the entrance of the bacillus in the small wounds that have but slight properties of resistance. General sanitary measures, individual cleanliness, which in plague and in other infectious diseases play such a great rôle in preventing the disease and causing its complete disappearance, are less active in the prevention of smallpox. The well-known, now so often tested, influence of cowpox vaccination is soon disregarded when for a long period smallpox no longer exists in a country and its terrors are forgotten. Vaccination is less carefully followed, the public looks upon it as a superfluous evil, agitators combat it, and the result is this, that in the course of years the percentage of smallpox morbidity increases among the population and it offers the most susceptible material for the production of an epidemic by a case brought from elsewhere.

VACCINIA, COWPOX, KINEPOX

BY J. C. WILSON, PHILADELPHIA

Definition.—An eruptive disease of the cow, communicable only by inoculation and causing, when transmitted to the human being, local reaction in the form of a pock and constitutional disturbances which are followed by a more or less lasting immunity against smallpox.

Natural cowpox is a rare disease. When it appears in a herd it is communicated from one cow to the others by the milkers. When the latter contract it, as is the case when cracks or abrasions of the skin upon the hands or fingers are present, the disease is termed casual cowpox. The disease propagated in infants and older persons by vaccination for the purpose of immunization against smallpox formerly constituted the chief source of the virus—humanized lymph. In recent years the disease is kept up by the systematic inoculation of calves and heifers in vaccine laboratories in which the lymph is prepared for commercial purposes—animal and bovine lymph. The nature of vaccinia, notwithstanding controversies and occasional experimental investigations extending throughout a century, still remains in doubt. On the one hand French observers—the dualists—entertain the opinion fully set forth in Brouardel's article in the *Twentieth Century Practice* that it is a disease distinct from smallpox and derived originally from the horse, which is liable to the disease in a generalized and epidemic form, as occurred at Rieumes near Toulouse in 1860. The experiments of Chauveau of Lyons are the mainstay of those who advocate the doctrine of the non-identity of variola and vaccinia. Briefly these experiments are as follows: A series of 30 animals were inoculated with cowpox virus. All of them developed a beautiful eruption. A second series of 20 animals were inoculated with humanized virus. Complete success resulted save in one instance. These 2 series of experiments gave distinct and unmistakable results and established the identity of cowpox and of vaccinia cultivated in human beings. A third series of 17 animals were inoculated with the virus of smallpox. None of the animals acquired cowpox. In every case small red papules developed which disappeared without leaving a scab. Fifteen of these 17 animals were subsequently vaccinated, 10 with the virus of genuine cowpox, 5 with humanized virus. Of these 15 animals, 1 showed a typical cowpox eruption, 3 imperfect vesicles and the remaining 11 no reaction whatever. The serum scraped from a papule caused by the inoculation of the virus of smallpox was inoculated into a non-vaccinated child and the result was a generalized confluent smallpox. A second child inoculated from the primary pustule of the first, developed a discrete smallpox. On the other hand the experiments of Ceely, King and others, referred to by F. D. Copeman in *Allbutt's System of Medicine*, establish the fact that the inoculation of smallpox matter into the udder or adjacent parts of the bovine animal—variolation—caused vesicles identical with or closely resem-

bling those of vaccinia, and that lymph from such vesicles, when not presenting the characters of the perfect vaccine pock which had been carried through a second or third remove in the cow or calf, gave results fully manifesting these characteristics; and when again transferred to man gave results not to be distinguished from the ordinary vaccine vesicle. In fact much of the lymph now in general use for purposes of vaccination is derived from such sources. Copeman, after a careful review of the facts, concludes that it may fairly be asserted that cowpox or rather that artificially inoculated form of the disease which we term vaccinia—is nothing more or less than variola modified by transmission through the bovine animal—an opinion very generally entertained among English and American students of the subject. Copeman suggests that “the most reasonable interpretation of such results may be that smallpox and vaccinia are both of them descended from a common stock—from an ancestor, for instance, which resembled vaccinia far more than it resembled smallpox.” The bacteriology of vaccinia, like that of variola has not yet been determined. Various observers have described micro-organisms. Klein and Copeman working independently demonstrated a small, short, almost oval bacillus sometimes present in considerable numbers. It is incapable of cultivation upon ordinary media, but may be grown in pure culture by employing for the purpose the hen’s egg inoculated with an emulsion of smallpox crusts in normal salt solution or glycerin incubated for about a month at the body temperature. Many observers have described bodies resembling psorosperms or protozoa. Peculiar ameboid bodies have been observed in the blood. Fresh vaccine lymph withdrawn before the maturity of the vesicle is a limpid fluid almost colorless in man and faintly straw-colored in the calf. It is faintly alkaline at first but becomes acid when stored. Microscopically it contains epithelial debris. Leukocytes are present in small numbers early in the development of the vesicle but they increase as the pock matures, rendering the lymph turbid or even puriform. A few red corpuscles are usually seen. Various bacteria may be demonstrated. When stored in capillary tubes for some time the lymph tends to become cloudy and cultivation experiments have shown that such lymph produces a larger number of colonies than recent lymph, which remains clear. This fact coupled with the knowledge that lymph which has been opaque is less certain in its action, justifies the assertion that turbid lymph should never be used in vaccination.

The **histology of the vaccine vesicle** has been studied in the calf by Kent. In the course of a few hours inflammatory disturbance occurs with cell accumulation and a fibrinous exudate. In this mass are numerous colonies of micrococci and in the blood vessels and cells are seen minute diplococci. Coagulation necrosis takes place in the cells of the rete Malpighii which become transformed into a network of trabeculæ, the meshes of which are distended with a fluid exudate forming a multilocular vesicle, the contents of which gradually become turbid. Later the trabeculæ break down and the vesicle is converted into a pustule. The fluid then undergoes desiccation and with the necrosed epithelium forms the crust. A new epidermis is formed underneath the crust by the proliferation of the cells of the surrounding Malpighian stratum. The extent to which the cutis vera has been implicated determines the depth of the scar.

VACCINATION

By J. C. WILSON, PHILADELPHIA

THE artificial inoculation of vaccine virus for the purpose of producing immunity against smallpox.

HISTORY

It is asserted by Humboldt that among the mountaineers of Mexico the protective power of cowpox against smallpox has been long known. Attention was called to the subject by Sulzer in 1713, and by Sutton and Fewster in 1761.¹

Jesty, a Dorsetshire farmer, in 1774, successfully vaccinated his wife and two sons from vesicles upon his own hands. A schoolteacher in Holstein, named Plett, vaccinated three boys in 1791. In Gloucester, Jenner's home, it was a traditional belief widespread among the people that those who acquired cowpox from milking cows affected from that disease were safe from smallpox. We must nevertheless recognize in Edward Jenner the discoverer of vaccination, perhaps the greatest boon that preventive medicine has given to the world. To his close observation, scientific reasoning and patient courage is due the establishment of this measure as a preventative of smallpox. Twenty years elapsed from the time the subject first engaged his attention until on May 11, 1796, he was able to submit the problem to a practical test. The story of inoculation of matter from the hand of the dairymaid, Sarah Nelmes, suffering from cowpox, into the eight-year-old lad, James Phipps, and the failure of the latter to develop smallpox after inoculation with the pus of that disease upon July 1st, is a familiar one. The encouragement of John Hunter, the publication of the famous "Inquiry into the Causes and Effects of the Variolæ Vaccinæ" in 1798, the immediate recognition of the value of vaccination, its prompt general adoption and more than a century of deliverance from a foul scourge, the honors conferred upon Jenner, constitute a brilliant episode in the peaceful progress of medical history.

Vaccination was introduced into America by Benjamin Waterhouse, Professor of Physic at Harvard College. He vaccinated on July 8, 1800, seven of his children. The matter attracted immediate attention and the method was introduced into Philadelphia by John Redman Coxe, who vaccinated his own child and subsequently subjected it to inoculation with smallpox virus, and into the Southern States through the influence of President Thomas Jefferson.

¹ *Vide Curschmann, Ziemssen's Cyclopedia, Amer. Trans., vol. ii.*

THE PRACTICE OF VACCINATION

Until recently arm to arm vaccination was very generally practised in order to perpetuate the lymph and secure its greatest purity. The use of crusts came into vogue at a later period. Within the last three decades bovine vaccine lymph has come into general use; and has the actual advantage over the arm to arm method of avoiding the opening of the vesicle and thus affording the opportunity for accidental infection and of wholly eliminating the danger of syphilis and other infections in the operation. When it becomes necessary to use human lymph it should be taken upon the eighth day from a typical unbroken vesicle in a perfectly healthy child at least three months old. The roof of the vesicle must be pricked at several points, care being taken not to draw blood. The lymph when not immediately used is preserved in a dry state upon sterilized "ivory" or bone points or slips. These points are preserved in bundles wrapped in gum tissue in well-stoppered bottles and in a cool place. When required for use the dry lymph is moistened by a few drops of warm sterilized water. Or the lymph is preserved in capillary glass tubes each containing the quantity required for one vaccination, sufficiently long to admit of sealing in the flame of a spirit lamp, thin enough to enable them to be thus instantaneously sealed and strong enough to be handled and transported without breaking.

Glycerinated Lymph.—It has been shown that the thorough incorporation of four parts of a sterilized 50 per cent. solution of chemically pure glycerin in water with 1 part of lymph or vesicle pulp and the storing of this mixture in sealed, capillary glass tubes, protected from light for some weeks is followed by destruction not only of the ordinary saprophytic bacteria found in the lymph, but also by the destruction of tubercle bacilli and the streptococcus of erysipelas added experimentally to it. Lymph thus treated is fully as efficient as ordinary lymph. By the method employed a sufficient quantity of material may be obtained from a single calf to perform from 2,000 to 5,000 vaccinations. It is distributed in tubes slightly larger than those used for ordinary lymph. These tubes are placed upon sale in boxes of 10, which contain also a bulb or tube, by means of which, when the ends of the capillary tubes are broken off, the lymph is expelled for use.

Vaccine produced by humanized lymph has in man a somewhat more rapid evolution than bovine virus and is attended with milder constitutional symptoms.

The Technique of Vaccination.—The outer surface of the arm near the insertion of the deltoid is usually selected. In infants the left arm is preferable. In females the outside of the leg just below the knee is sometimes chosen. The surface should be washed with warm water and soap, dried with a soft towel and the lymph inserted by puncture, multiple superficial crossed incisions or after the removal of the epidermis by scraping. The spots should be rendered moist by the exuding serum but care should be taken not to draw blood. For this purpose a thoroughly sterilized old-fashioned thumb lancet or an ordinary flat-headed surgical needle should be used. Vaccination should be performed at two points about an inch apart and the diameter of

the abraded or scarified area should be one-third of an inch. The clothing should not be replaced until the serum has dried. A thin layer of sterilized cotton or lint may be lightly applied and held in place by means of rubber adhesive plaster not encircling the limb. This should be from time to time renewed. The pock should be kept uninjured, dry and clean, and may be occasionally lightly dusted with starch or ordinary toilet powder. The new born should be vaccinated only at times of the prevalence of small-pox. Children are commonly vaccinated during the course of the third month. If failure ensues the operation should be repeated. Persons exposed to the contagion of smallpox should be immediately revaccinated. The immunity conferred diminishes with time. Revaccination should be performed at the seventh year of age, again at puberty and from time to time as local epidemics occur.

Typical Vaccination.—There is a little local irritation which passes away. The period of incubation varies from three to five days. At the end of this time local reaction shows itself in the form of one or more reddish papules at the point of inoculation. These in the course of the next five days develop into compound vesicles, the contents of which are at first clear but later, owing to the increase in the cellular elements, become opaque. By the eighth day the vesicle has attained its full development. It is round or oval with prominent and well defined edges and a depressed or umbilicated centre. About the tenth day an extensive erythematous areola usually develops and the contents of the pock have become purulent. The surrounding skin is swollen, indurated, tender. At this time scabbing begins at the centre of the pock and rapidly extends toward its borders. The areola subsides about the end of the second week, and the pock is converted into a thick brownish crust which gradually becomes dry and hard and separates between the twentieth and twenty-fifth day from the vaccination, leaving a scar at first of a dusky red color but gradually becoming white and pitted or foveated. The corresponding superficial lymphatic glands, namely, the axillary or inguinal, as the case may be, become enlarged and tender.

The constitutional reaction is commonly slight. It consists of moderate fever, restlessness at night, loss of appetite and irritability. These phenomena usually occur upon the third or fourth day and may continue until the early part of the second week. Erythema, roseola, or urticaria may develop at any time during the course of the vaccine disease. These eruptions are usually transient. Leukocytosis shows itself about the third day coincidently with the appearance of the local eruption, and again about the time the pock reaches maturity. The resulting immunity against vaccinia as that against variola varies in duration in different individuals. In rare instances it is permanent, but as a rule successful revaccination may be performed in the course of some years. The pock of revaccination, however, lacks in most instances the typical development of the primary vaccine lesion. The constitutional reaction in revaccination is sometimes severe. If no characteristic lesion follows the attempt at revaccination, the operation should be repeated once or twice at short intervals.

ATYPICAL VACCINIA IN MAN

1. Variations in the Number of Pocks.

a. Supernumerary pocks not infrequently develop in the vicinity of the original vaccine lesion.

b. Confluent pocks are in rare instances formed by the coalescence of the supernumerary pocks either among themselves or with the original lesions.

c. Generalized vaccinia or vaccinal eruptive fever is less common. It consists of a generalized vaccine rash developing in various parts of the body, especially about the wrists or on the back. Secondary pocks usually begin to develop about the eighth or tenth day after vaccination and are often more abundant on the vaccinated limb than elsewhere. The pocks appear in successive groups so that they may be seen in all stages of development. The disease may last several weeks. It is a serious affection and sometimes in children terminates in death.

d. Vaccinal eruptions generalized by autoinoculation. Supernumerary pocks may be produced by scratching with the nails after they have been in contact with the ruptured vaccine pock. They may occur in any part of the body and vary from one or two to many. The number is sometimes very great. They have been observed upon the cheek, lips, tongue, buttocks, breast and the genital organs. When they occur on the mucous surface of the vulva the resulting ulceration may, if proper caution is not exercised, give rise to the suspicion of venereal disease.

e. Local vaccinal eruptions sometimes confluent may arise at the seat of previously existing cutaneous lesions, as impetigo, eczema, acne or psoriasis.

2. Variations in the Size of the Pocks.

a. Two or more of the primary vesicles caused by vaccination may coalesce to form one large pock.

b. The size of the pock may be increased by coalescence of supernumerary pocks in the immediate neighborhood. Acland has recorded an instance in which a sore on the arm thus produced measured 4 inches by $4\frac{1}{2}$ inches.

3. Variations in the Contents of the Pock. In cachectic individuals the contents of the vesicle, instead of being clear and limpid at the end of the first week may be watery, hemorrhagic or purulent.

4. Variations in the Evolution of the Pock.

a. Acceleration. The pock develops more rapidly in warm weather than in cold. Its evolution is hastened in some instances apparently by the idiosyncrasy of the individual and to some extent by the character of the lymph employed. Cory found upon vaccinating in series that, insertion being made on each of eleven successive days, all the successful insertions came to maturity upon the ninth day. The insertions made subsequent to that day failed.

b. Retardation. Cases have occurred in which aborted vesicles have become active after revaccination, a week or more after the original insertion.

c. Abortion. The non-development or abortion of the pock is determined by the immunity of the patient, the quality of the lymph and the skill of the vaccinator. In revaccination a bright red papillary lesion, described as the

“raspberry excrescence,” sometimes develops about a week after the insertion of the lymph. Vesicles do not form, the papules remaining hard and dense for several weeks. There is no areola, and healing ultimately takes place without the formation of a scar.

5. Variations in the Involution of the Pock. These are determined by vaccinal injuries. Secondary infection may take place at the time of the operation or subsequently, especially if the pock is injured. It may be the result of the use of contaminated lymph or infected instruments or may arise at a later period from other causes. It cannot be urged that vaccination is free from the liability to accident. Intense inflammation, suppuration, extensive deep-seated ulceration or gangrene may occur in neglected cases. Erysipelas is not a rare complication. Cellulitis, abscess and septicemia also occur. None of these accidents are however peculiar to vaccination. They may arise in any local lesion of the skin in the absence of cleanliness or of proper antiseptic measures.

6. Variations in Healing and the Formation of Scar. The lesion of the skin caused by vaccination is usually well healed by the end of the third week. It may, however, remain open for weeks or months. The scar, instead of showing the usual circumscribed, slightly depressed foveated appearance, may manifest hypertrophy or puckering of the skin or run into keloid.

7. Transmission of Chronic Specific Disease by Vaccination.

A. Vaccination and Syphilis.—Vaccino-syphilis.—Syphilis has been transmitted by vaccination but the number of well authenticated instances is few. Now that the introduction of bovine lymph has become universal invaccination syphilis is a remote possibility. It may however occur in consequence of the direct contamination of the lymph taken from an individual suffering at the time from syphilis or to accidental contamination of the instrument or wound or to infection from the vaccinator. The sequence of events is as follows:

If the subject be susceptible to vaccination the pocks may show no departure from the normal course, but in some instances they abort. If they be irritated, the vaccinal sore may become inflamed, suppuration may occur and the ulcers may scab over and again break out. Whether the vaccination runs a typical or an atypical course, a chancre with indurated base eventually forms at the point of inoculation. The well-known case of R. C., a medical man, throws valuable light on the subject.¹ R. C. purposely vaccinated himself on four occasions from children known to be syphilitic. First, in 1887, the vaccination was successful but the pock matured early and declined after the third or fourth day. No syphilitic lesions ensued. Two years later he again vaccinated himself from a syphilitic source. Neither vaccinia nor syphilis followed. Eighteen months later he repeated the experiment but the results were negative. Finally, upon the fourth occasion, he was vaccinated in three places from a child, obviously the subject of congenital syphilis.

The following table gives the symptoms and dates in a case of invaccinated syphilis, R. C., fourth experiment.

¹ *Vide* A System of Medicine, edited by Clifford Allbutt, vol. ii, p. 607 *et seq.*

STAGE.	DATE.	SYMPTOMS.
Primary.	1st day, July 1, 1881.	Inoculation in three places on left forearm.
	8th day.	Arm healed.
	21st day.	Papules at points of inoculation.
Secondary.	35th day.	Earliest appearance of ulceration.
	38th day.	Chancres of ordinary syphilitic type at one point of inoculation. Parts inoculated excised.
	44th day.	Glands first noticed to be enlarged.
	45th day.	One wound indurated.
	47th day.	Sore throat.
	54th day.	Pains in limbs.
	57th day.	Roseolous eruption lasting four days only.
	88th day.	Acne chiefly on back.
Tertiary.	21 weeks.	Indurated mass began to form on left thigh (gumma). This inflamed and broke down.
	23 weeks.	Two gummas and a little later tenderness over tibia (? periostitis).
	7 months, 1882.	Sore throat, other symptoms better.
	7½ months.	Headache.
	8 months.	Acne spots fading, wounds of gumma healing.
	8-13 months.	Some occipital headache, worse at night. Pupils unequal, right generally the smaller.
	14 months.	Tingling in right hand. Vertigo. Tingling right foot, intermittent at first, then constant.
	15½ months.	Loss of power on right side.
	September 17, 1882.	Slight aphasia.
	1-2 years.	Symptoms gradually passed away. No evidence of syphilis two and one half years after inoculation.

Acland makes the following deductions from the case, which are in entire accordance with general observation.

a. That vaccination can be successfully performed with lymph taken from a source tainted with syphilis without necessarily communicating the disease.

b. That if syphilis be communicated in the process of vaccination it does not follow that all the points of insertion will become infected.

c. That the evolution of syphilis, as regards the primary and secondary stages, is not necessarily disturbed, that it is neither accelerated nor retarded by simultaneous vaccination.

d. That no care in the selection of lymph obviates the risk of vaccinating from an obviously tainted source.

e. That when syphilis is communicated by vaccination, the first appearance of the disease is at the seat of puncture; and that there is no evidence of general infection until a much later period.

B. Vaccination and Tubercle.—Acland holds that from the facts adduced to the present time the communication of tuberculosis as a result of vaccination is of such exceeding rarity that it may be doubted whether it has ever occurred. In well-regulated vaccine laboratories the animals used are previously submitted to the tuberculin test. It has been suggested that the animals employed should after the collection of the vaccine material, be

slaughtered and submitted to post mortem examination. In case of the presence of tuberculous lesions, the vaccine material should be rejected.

In some few instances lupus has been observed at the seat of vaccination. There is room to believe, however, that it has been due to the patient's constitutional tendencies rather than to invaccination. There are no facts to support the assertion of the antivaccinationists that tabes mesenterica and "scrofula" have been increased by the practice of vaccination.

C. Vaccination and Leprosy.—The alleged cases of transmission of leprosy by vaccination are open to serious doubt (Acland).

D. Vaccination and Cancer.—Acland states that there is no authentic case on record in which cancer has resulted from vaccination, nor is there any recorded case of cancer developing in the vaccination scar.

E. Vaccination and Tetanus.—The vaccine lesion, like any other wound of the skin, may render the patient liable under certain circumstances and the absence of proper precautions to the infection of tetanus. A limited number of cases of fatal tetanus developing after vaccination are reported.

Acland has arranged the dates at which various eruptions or complications may be looked for after vaccination, as follows:

1. During the first three days: Erythema; urticaria; vesicular and bullous eruptions; invaccinated erysipelas.

2. After the third day and until the pock reaches maturity: Urticaria; lichen urticatus; erythema multiforme; accidental erysipelas.

3. About the end of the first week, and generally after the maturation of the pocks: Generalized vaccinia—(a) by autoinoculation, (b) by general infection; impetigo; accidental erysipelas; vaccinal ulceration; glandular abscess; septic infections; gangrene.

4. After the involution of the pocks: Invaccinated diseases, for example, syphilis.

THE RESULTS OF THE GENERAL PRACTICE OF VACCINATION

"Vaccination duly and efficiently performed" in infancy, with revaccination at the age of puberty, constitute an almost complete protection against smallpox. In cases in which smallpox occurs after this, the disease is so modified that it becomes a trifling malady. In the period prior to vaccination, smallpox was essentially a disease of childhood. Since vaccination has become general, it has lost this peculiarity. With the gradual extension of vaccination there has been, according to the Forty-third Annual Report of the Registrar-General of Great Britain, first, a gradual and notable decline in the mortality from smallpox at all ages. Second, this decline has been exclusively among persons under ten years of age and most of all among children under five. Thirdly, that after the age of ten, the mortality, so far from having declined, has actually increased—very slightly among persons from ten to fifteen years of age, but very greatly among persons older than this; and, lastly, that the increase has been greater the more advanced the time of life. The explanation of these facts is to be found in compulsory vaccination in infancy and the general neglect of revaccination at the proper time.

The French Minister of War, M. de Freycinet, in 1890, made the following statement: "One now sees not only in France but in Algiers, in Tunis and in Tonquin, the army protected by the strict application of compulsory vaccination. . . . I cannot forget that in 1870-71 the German Army, counting 1,000,000 vaccinated and revaccinated men, only lost 459 men from smallpox in the two years, whereas our army, far less numerous, had from the same cause a loss of 23,400 men whom the prescient application of revaccination might have saved for the service of France." As a matter of fact vaccination and revaccination have stamped out smallpox in the German Army. The immunity of doctors, nurses and others in smallpox hospitals, abundantly proved by the statistics, is due to the systematic revaccination of such individuals. Communities in which vaccination and revaccination are systematically practised are as a matter of fact immune from outbreaks of smallpox. Only the small contingent of individuals who have neglected or evaded revaccination are liable to the disease. On the other hand, communities in which through ignorance, indifference or the activity of antivaccinationists the opportunities of protection have been persistently neglected, suffer from occasional more or less extensive and disastrous outbreaks.

VARICELLA, CHICKEN-POX

By J. C. WILSON, PHILADELPHIA

AN acute infectious, endemic and epidemic disease of childhood characterized by mild constitutional symptoms and a vesicular exanthem which develops in irregular successive crops.

HISTORY

Chicken-pox was formerly confused with smallpox, and until recently there have been those who regarded it as a greatly modified and very mild variety of smallpox. It is now generally regarded as an entirely distinct disease. One of these diseases never gives rise to the other. The attack of one confers no immunity against the other, and it is no uncommon thing for an individual who has recently suffered from one to contract the other; vaccination affords no protection against varicella, and children who have recently suffered from varicella react to vaccination in the ordinary manner.

ETIOLOGY

a. Predisposing Influences. Varicella is a widespread disease, endemic in the great centres of population, and frequently becoming epidemic, usually in the autumn or early spring. As in the case of other readily transmissible infections, sporadic cases occur and frequently become the centre of house epidemics or extended outbreaks. The liability is general, and scarcely any individual who has not already had the disease, escapes when it makes its appearance in a school or other public institution. The disease is benign, the epidemic almost always mild. It is peculiarly a disease of childhood, the majority of cases occurring before the eighth year and few after the tenth. It is comparatively infrequent during the first year and, though rare, occasional cases, of which I have seen several, occur after puberty. Sex is wholly without influence as a predisposing factor.

b. The Exciting Cause. The specific pathogenic principle is not known. The disease is highly contagious and usually communicated in the ordinary intercourse of children in the family, the school or the playgrounds. The poison is eliminated by the expired air, from the surface of the body and in the exfoliation of the crusts. It doubtless enters the body by way of the respiratory passages. Direct contact is not necessary, the infection being com-

municable to some little distance by the air and more remotely by persons not contracting it who pass from the sick to those who are susceptible, and finally by means of fomites. Inoculation experiments have shown that it is present in the contents of the vesicles. Outbreaks of varicella are sometimes associated with measles, whooping-cough, scarlet fever or variola.

SYMPTOMS

The period of incubation varies from ten to nineteen days. It is usually thirteen or fourteen days. On three occasions in which I was able in private practice to determine accurately the day of exposure, the eruption appeared upon the thirteenth day. Steiner found the incubation after artificial inoculation to be eight days.

Prodromes as a rule do not occur. In many of the cases the eruption is the first sign. There may be pallor, fretfulness, loss of appetite and slight fever. The severer cases may begin with vomiting, chilliness, headache and pain in the back and legs. These symptoms are, however, uncommon. The eruption first appears usually upon the face and spreads into the hairy scalp and progressively over the trunk and extremities. It sometimes comes out first upon the back and shoulders and very often at the same time upon the wrists and forearms. No part of the body remains free from the pocks, but they are more numerous upon the trunk and upon the upper than upon the lower portions. The rash consists of small red scattered flat papules circular or ovoid in shape, which rapidly develop into vesicles. They usually come out in irregular crops, fresh spots continuing to appear among the older, so that by the fourth or fifth day they are seen in all stages of evolution and involution. The later papules are less abundant than the first crops and do not form such perfect vesicles. Some few of the papules do not develop into vesicles at all but undergo complete resolution in the course of several hours. Nearly all of them develop in an equally short period of time into vesicles which are fully formed within twenty-four hours. Not infrequently the papular stage is so brief that the fully developed vesicle appears upon skin that shortly before seemed entirely normal. The vesicles are usually at first hemispherical and appear to be superficially situated in the skin. Their contents are limpid, so that they sometimes present the appearance of a drop of clear or faintly yellowish fluid resting upon the surface. In the course of a few hours they become milky and then sero-purulent from admixture with round-cells, and in a further brief period desiccation takes place with the formation of flat, yellowish-brown firmly adherent crusts, which separate in about a week, leaving in the majority of instances no scar. The vesicles are readily ruptured by scratching and other injury. Under these circumstances, and when the lesion approaches more nearly to that of variola and involves the deeper structures of the skin, pitting may result, especially upon the face. This deformity gradually becomes less conspicuous and usually in the course of time disappears. It is probable that spontaneous rupture of the vesicles does not occur. The pock in varicella commonly has little or no areola, but in the severer cases, marked infiltration and hyperemia of the surrounding skin may here and there be seen.

The diameter of the vesicles varies from 1 to 15 or 20 millimeters: their number from ten to several hundreds. They are in most cases discrete but when very numerous, confluence may often be discovered upon careful search. Primary umbilication does not occur, but as desiccation takes place a depression in the centre of the crust—secondary umbilication—is sometimes seen. The eruption occurs upon the mucous membrane of the mouth. In very rare instances it has involved the larynx. It is rare also upon the conjunctivæ and upon the labia and prepuce. In these situations the development of the vesicle is the same as upon the skin, but under the influence of warmth and moisture the wall is rapidly destroyed and the lesion converted into a circumscribed superficial ulcer. An erythematous blush may precede the eruption. The peripheral lymph glands are not infrequently slightly swollen and tender. In the lighter forms there is little or no elevation of temperature during the whole course of the disease; in the more severe cases fever, if not already present develops with the rash, to the abundance of which it bears, however, no constant relation. It commonly subsides in two or three days and very seldom lasts a week. It does not conform to type.

The *duration of the attack* is variable. Three or four weeks may elapse before the separation of the last crusts. Relapses do not occur.

The immunity acquired is in most instances permanent. In rare cases subsequent attacks have been observed.

The **anomalies** of the disease relate to the rash. In rare instances some of the vesicles contain blood with ecchymoses and bleeding from the mucous surfaces—Varicella hemorrhagica; still more rarely they develop into bullæ like those of pemphigus or ecthyma—V. bullosa; in cachectic children some of the skin lesions may become extensively ulcerated or even gangrenous, and death occur as the result of exhaustion—V. gangrenosa vel escharotica.

COMPLICATIONS AND SEQUELS

In rare instances an acute nephritis with the characters of post-scarlatinal nephritis has been observed. Erysipelas, gangrene of the vulva and scrotum and septic arthritis are rare complications. There are no special sequels. Palsies may occur as the result of peripheral neuritis.

DIAGNOSIS

The direct diagnosis of varicella in cases seen from the beginning is easy. The mildness of the initial symptoms, the persistence of fever, if present at all, upon the appearance of the eruption, the character of the individual pock which is essentially vesicular, its rapid evolution, the absence of primary umbilication, the appearance of the lesions in irregular crops so that papules, vesicles and crusts are seen at the same time in the same region are of diagnostic importance. Varicella is usually endemic in cities; variola occasionally epidemic.

The differential diagnosis principally relates to the discrimination of varicella from smallpox, and the chief points are indicated in the foregoing paragraph. It is of great practical importance. In smallpox the onset is abrupt; the fever high; headache and backache intense. The rash appears

about the third day with remission of fever; its evolution is tardy, and by the progressive stages of papule, vesicle, pustule and crust. The papule is hard, shot-like and deep-seated, and there is primary as well as secondary umbilication. There are cases in which at the period of desiccation, the differential diagnosis cannot be made.

The resemblance of urticaria, pemphigus and other diseases of the skin to varicella is remote.

PROGNOSIS

Varicella is a benign affection. Convalescence is in the majority of cases uneventful and complete. In rare instances death has resulted from nephritis, sepsis or laryngitis. Fürbringer reported a case, in an undoubted epidemic of varicella, fatal without important complications, in consequence of the intensity of the infection, and Nisbet a death from the intensity of the eruption. But these accidents are wholly exceptional.

TREATMENT

a. **Prophylaxis.**—Isolation should be practiced in schools and asylums. In the home it is unnecessary to attempt it save where there are sickly or feeble children. The quarantine should be prolonged until the last crusts are thrown off. Disinfection of the person, clothing, and apartment is desirable in order to minimize the danger of spreading the disease.

b. **The Management of Cases.**—In the majority of the patients no special treatment is necessary. The febrile cases are to be kept in bed and managed in accordance with the plan laid down for the milder cases of measles or for rubella. The urine should be systematically examined for albumin. Locally, carbolized and warm baths are useful to relieve the itching; applications of oil may hasten the separation of the crusts, and scratching may be prevented by the use of mittens.

ERYSIPELAS

By A. SCHÜTZE, BERLIN

SINCE the development of modern bacteriology and the classical investigations of Robert Koch regarding the etiology of infectious diseases due to wounds, our views and opinions regarding these diseases have been completely changed in the past quarter of a century as a result of these teachings which have impressed themselves upon our knowledge. Whereas in the pre-bacteriologic era the conception of infection was confused, and curious views were associated with it, we now know that infection is the expression for a distinct pathological process which is produced by a specific cause, and we have already learned to recognize with certainty a great number of diseases due to such agents. Thus, for example, there is no tuberculosis without the tubercle bacillus, the typhoid bacillus is the only cause of enteric fever, and the comma bacillus that of Asiatic cholera, bacteria which, by their destructive activity in the organism and by the generation of products of metabolism, produce the pathologic picture in man, the recognition of which in its developed clinical symptom-complex has been the common property of physicians since ancient times. It is this law of the course and nature of infection which is a triumph of our modern medicine and the fruit of profound study and animal experiments. We owe this particularly to the last two decades having their scientific foundation and support in the labors carried on during the seventies and the beginning of the eighties of the last century, which were to become authoritative and epoch-making in our entire subsequent bacteriologic investigations.

If we cast a retrospective glance over the literature of this time, we meet, besides other similar diseases, particularly one infectious disease which covers a comparatively broad space and which has been the starting-point of many bold endeavors and investigations. The reason for this phenomenon may be seen in the fact that in the affection with which we are concerned in this chapter, in the majority of cases, not, as for example, in enteric fever or in tuberculosis, there is a pathological picture which is complicated, clinically, extraordinarily often many-sided, and for this reason difficult in regard to its experimental investigation, but which, because it concerns a process which is localized to the external skin, respectively to the mucous membrane, is clearly developed and for this reason is more susceptible to bacteriological investigation, and the course of which is usually connected with definite rules.

By **erysipelas**, **rose**, or **St. Anthony's fire**, we understand an acute infectious disease, beginning with fever, which, by a peculiar, always sharply defined inflammatory swelling and reddening of the external skin or of the natural openings of the body, or of the mucous membrane of the normal cavi-

ties of the body, often shows a conspicuous tendency to rapid distribution. We know that erysipelas is due to the action of a special microorganism, which will be described later on, which enters the damaged skin, giving rise to a familiar clinical picture known to antiquity, in the same form in which it presents itself to us to-day. Thus, we read in the works of the Greco-Roman and Arabian physicians, descriptions of the symptoms and the course of erysipelas, which in the main correspond to our experience in most particulars, although naturally, at that time, the difference between the affection in the purulent and in the gangrenous forms was not sharply defined. In the writings of Hippocrates we find a distinct differentiation between traumatic and idiopathic erysipelas, which is even retained to-day, and in Galen we find the view expressed that erysipelas and phlegmons present different morbid processes.

ETIOLOGY

Regarding the **origin of erysipelas**, the view was formed among most physicians, particularly by the labors of Wernher, Velpeau and Trousseau, that it was a contagious disease, and due to a specific toxic product which need only enter a slightly damaged cutaneous area to produce its effects. The view expressed by Henle in 1840, that very probably we would find the causative factor of many contagious diseases in the lowest vegetable organisms, was expressed by Hüter in the case of erysipelas in a somewhat clearer and more concise form, in that this author promulgated the view that in erysipelas the condition was due to an invasion of schizomycetes. And, in fact, Nepveu and Wilde succeeded in demonstrating micrococci in the blood of erysipelas patients, these being met with particularly profusely in tests in which the blood was taken from the cutaneous areas affected by erysipelas. A further progress was due to the experiments carried on by Orth, in the year 1873, in the transmission of erysipelas, in that this investigator subcutaneously injected into a rabbit the contents of an erysipelas vesicle in which numerous curved bacteria were present. An inflammation entirely analogous to erysipelas was now produced, which could be propagated by obtaining the edematous fluid from the subcutaneous tissues of this animal and transmitting it to a second rabbit, in the edematous cutaneous areas of which bacteria could again be demonstrated in plentiful numbers. After this, the investigations of v. Recklinghausen and Lukomsky revealed the interesting fact that the lymph vessels and channels of the skin limiting the erysipelatous area are filled with micrococci. This observation was confirmed by Billroth and Ehrlich, and in the succeeding investigations by Tillmans and Letzerich this was settled and amplified, they having found micrococci in inoculated erysipelas in the wound due to inoculation, in the blood vessels, muscles, liver, spleen and kidneys. The classical investigations of R. Koch (1878) must be mentioned in this connection, who, by inoculating the feces of mice into the ear of a rabbit, produced an erysipelatous process, with redness and swelling. Upon microscopical investigation, in the entire extent of the cutaneous area, Koch found bacilli which had distributed themselves upon both sides of the entire cartilage of the ear in a net-like manner, and he looked upon these microbes as the unquestioned cause of the disease.

But as instructive as the above-described experiments were, a large part of them, such as those of Billroth and Ehrlich, Lukomsky and Tillmanns, were faulty, a fact which was admitted by the authors themselves, in that, in their investigations, particularly phlegmonous or pyemic cases were concerned, therefore, none of them being pure, uncomplicated ones. The exact proof that in all cases of erysipelas we are dealing with an invasion of streptococci, and that erysipelas in all its forms and manifestations is constantly due to the streptococcus, we owe to Fehleisen, who, in contrast to Lukomsky, *never* found his micrococci in the blood vessels, but exclusively in the lymph spaces and channels of the skin, and who, in accordance with the newly founded laws of Koch, first cultivated the causative factor of erysipelas by the use of a solid culture medium in pure culture, and for this reason designated the microorganism as the streptococcus erysipelatos. Fehleisen proceeded in the following manner, that after carefully cleansing and disinfecting the surface of the skin, by means of scissors which had been heated and allowed to cool he removed particles of skin, which he placed in nutritive gelatin and upon blood serum, and, finally, after numerous failures at a temperature of 40° C., he placed them in a melted infusion of meat gelatin to bring them into the closest possible contact with the culture media. After the culture tubes were exposed for two hours at a temperature of the incubation oven and the gelatin had become solid, it was kept for two days at a temperature of 20° C. At the point of inoculation small white points became visible, which enlarged slowly and finally formed a delicate white coating. By transferring these colonies, which were proven by microscopic examination to be a pure culture, to a number of other gelatin tubes, in from twenty-four to thirty hours fine white specks formed, which soon coalesced and finally covered the entire inoculation passage in the form of an opaque white sod. Fehleisen, who strictly differentiated erysipelas and phlegmon and who limited the pathologico-anatomical and bacteriological studies alone to true uncomplicated erysipelas, now, upon the basis of his careful investigations, came to the conclusion that the micrococcus which is always found in erysipelas, being exclusively disseminated by the lymph channels, this being peculiar to it, was morphologically different from other cocci which resembled it, in that these placed upon suitable artificial culture media showed quite different conditions of growth so that, according to Fehleisen, a confusion with erysipelas cocci could be excluded.

It was, however, necessary, according to Koch, in order to show the absolute proof of the pathogenicity of an organism, that the streptococcus obtained by pure culture also possesses the property of producing true erysipelas after transference to other individuals. First these investigations were carried on in rabbits, and in fact by means of inoculation of these animals, which in from thirty-six to forty-eight hours after the injection showed a rise in temperature of from 2° to 4° F., at the point of inoculation, and beginning there a sharply defined redness about the ears was produced, which distributed itself in the course of the veins, rapidly reaching the root of the ear, and after declining, in this area, in about three days advanced to the head and neck. From the duration and course of the entire process, which lasted from six to ten days and ended favorably, as well as from the microscopical findings

which corresponded completely with those found in man, Fehleisen believed the identity of the process produced in the rabbit with erysipelas of man to be proven. He characterized the true erysipelas in the rabbit by the sharply defined wandering redness, by the succeeding healing of the point of the inoculation without reaction, by the absence of suppuration and abscess formation and by the rapid and complete restitution of the tissue, in contrast to pseudo-erysipelas produced by decomposing fluids. In the same manner as in animals, Fehleisen in v. Bergmann's clinic was capable, in man, that is in five patients with inoperable carcinoma and in one patient suffering from lupus, of producing a typical attack by means of a pure culture of streptococci inoculated for therapeutic purposes, a process which will concern us further on. The affection began with fever, chills and the well-known accompanying phenomena, by a sharply limited and slightly raised erythema, as well as by a tendency to gradual healing, all conditions characteristic of erysipelas. This experiment of Fehleisen was the missing link in the chain of proof that the streptococcus erysipelatos was the pathogenic organism and the true causative agent of erysipelas, which in its morphologic as well as its biologic properties differed from other micrococci especially from the streptococcus pyogenes.

Although this assumption of the specificity of the streptococcus erysipelatos was confirmed by Rosenbach, who pointed to the morphologic differences of the streptococcus erysipelatos and streptococcus pyogenes, decided doubts soon arose regarding the correctness of this teaching; thus Hajek and especially v. Eiselsberg and E. Fränkel in several cases were able to produce true erysipelas with phlegmonous and peritoneal pus obtained from cultures by inoculation in the ear of a rabbit, which in a histological examination coincided completely with the picture described by Fehleisen. To these were added the investigations of Widal, who showed that the streptococcus of erysipelas only produced erysipelas, the streptococcus pyogenes usually produced suppuration, revealing the varying virulence of the same streptococcus. Thus he was able to show that the streptococcus pyogenes, which after an intravenous injection was able to kill a rabbit, being obtained in pure culture from the blood of the heart of this animal, constantly produced erysipelas in the ear of the rabbit. On the other hand, suppuration has been produced experimentally with certainty, by the streptococcus of erysipelas, as we know from the investigations of Hoffa, v. Eiselsberg, Simone, v. Noorden, and others. We see, therefore, that by means of these investigations, grave doubts arose regarding the specificity of the coccus of erysipelas. However, the strict proof which would have been final for the untenableness of this view, regarding the specific nature of the microorganism in question, namely that also streptococci which were due to non-erysipelatos pathological foci of man were capable, upon inoculation in other human beings, of producing a typical erysipelas had not yet been brought forth. To decide this question Petruschky inoculated two patients suffering from carcinoma with a pure culture of streptococcus obtained from fresh peritoneal pus, producing a typical erysipelas, which rapidly spread over the chest and neck and ran its course with high fever. Therefore, in this manner in full coincidence with the above-named animal experiments, the proof was furnished that the coccus of erysipelas is not to be regarded as the specific agent of erysipelas but that typical erysipelas may

also be produced in man by cocci which are not obtained from a case of erysipelas. We now know that one and the same streptococcus may produce erysipelas as well as suppuration, regardless which of these two processes is the primary one, and that this knowledge is of extraordinary value clinically on account of the intimate connection existing between puerperal sepsis and erysipelas, for the view exists that both affections may owe their origin to the same streptococcus, which, according to its virulence, individual and local effect, as well as the resistance of the organism, may produce either a mild or a severe clinical picture. Further animal experiments by Jordan, Felsenthal, and Petruschky have shown that it is possible by inoculation with the staphylococcus aureus to produce a typical erysipelas in the ear of a rabbit; however, some time previously some Italian investigators, Bonome and Bondini-Uffreduzzi, had described a case of staphylococcus erysipelas. Petruschky, further, in connection with Delius, in Koch's Institute, succeeded with various varieties of the bacterium coli commune, particularly with some originating from human cystitis in producing a typical erysipelas in the ear of the rabbit, and Neufeld in his experiments with Fränkel's pneumococcus found this organism very suitable for the production of erysipelas in the ear of the rabbit.

In considering the question in what manner erysipelas **infection** occurs, we must admit that the pathogenic agent only enters the organism by a rupture of continuity and that the disease by this peculiarity, as well as on account of its great tendency to relapses, which will be described later on, differs from the exanthemata with which it was formerly grouped. The fact has been well known for a long time that under all circumstances erysipelas takes its starting point from injuries of the external skin or mucous membranes although, naturally, the importance of the lesion which represents the point of entrance for the microorganism is an extraordinarily varying one. Whereas in the one case we find large and gaping wounds which are responsible for the entrance of the pathogenic agent, in other cases there are apparently only very slight and very unimportant injuries which can only be determined by the most careful investigation, in some circumstances injuries which have healed in twenty-four hours without leaving a trace, for an example, needle-pricks, remains of scratchings, erosions, and the like. This observation, that erysipelas shows a special preference for wounds and frequently takes its starting-point from small ruptures of continuity, Hippocrates had already noted, and he particularly emphasized that even in careful treatment of infected wounds erysipelas may arise, so that blame need not necessarily be attached to the physician because of a sudden appearance of this affection. In the course of years, however, the view gradually gained ground that, primarily, faulty care and nursing was the cause of the appearance of the disease. In fact we well know from reports by Boinet, Wells, Seere, Billroth and Waeckerling, Ponfick, Volkmann and others, that there were certain hospitals, and that there were even individual wards in these hospitals in which every patient operated upon was regularly attacked by erysipelas and that it was often even possible to refer the origin of these endemics to an individual case, to one and the same bed, even to a particular article (the covering of an operative suture, König). But even in modern hospitals, erected according to all

rules of hygiene, well ventilated and scrupulously clean, as well as in prisons, garrisons, upon hospital ships and in certain districts of cities, as in Boston, Bonn, Edinburgh, Oxford, etc., such epidemics have been observed.

According to the reports of Hirsch, in the years 1822 to 1836, erysipelas occurred in 70 different epidemics in North America and in the year 1841 it appeared in a pandemic form with a malignant typhoid character.

Although no decided effects can be attributed to *climatic influences* upon the development of erysipelas, which appears over the entire earth, only being somewhat less frequent in the tropics and in Japan, it must be emphasized that in the severer periods of the year, and particularly during damp cold seasons, and at times of sudden variations of temperature, it occurs decidedly more frequently than during the hot summer months.

Regarding the **mode of transmission**, we know that the patient with erysipelas, if he is not sufficiently isolated and kept apart from others, even in rooms which have been previously free from erysipelas and during times free from epidemics, these may readily be a source of infection for his neighbor, for relatives, physicians and nurses, as has been proven by numerous accurate investigations. Further, particularly by reports from former periods, as well as by the inoculations purposely carried on for curative purposes, we have learned that a direct transmission of the disease by means of infected instruments and bandages is possible.

SYMPTOMS

Regarding the **period of onset and course of erysipelas**, it may be said in general that a prodromal stage is absent and that the period at which the infection by the streptococci of erysipelas occurs is not characterized by a conspicuous symptom, so that regarding the *period of incubation* in man, we only know what we have learned from artificial transmission experiments. According to these, the duration varies from fifteen to sixty-one hours; in some cases, however, erysipelas only appears in from six to eight days after the injury, without our being able to determine a distinct relation between the incubation and the severity of the disease. When erysipelas occurs as a primary disease in previously healthy patients, in those in whom fever has not existed, there being no decided distinction regarding age, sex and constitution, the affection is usually ushered in by a more or less severe chill, not infrequently accompanied by vomiting, to which at once a decided rise in temperature is added. If, on the other hand, erysipelas occurs as a *secondary affection* in a previously existing febrile disease, if we note the affection, for example, in connection with scarlatina, or sepsis, in the majority of cases no well developed chill can be recognized and the temperature which in primary erysipelas even upon the first days rises to 104° F., in the case of a phthisical patient whose temperature varies between 99.5° F. and 101.3° F. it will perhaps be raised only from 1 to 2 degrees, so that the onset of erysipelas in these cases will often remain unrecognized; this we are able to confirm from our own experience. It is, therefore, necessary in such patients in whom the diagnosis cannot be definitely made from local symptoms, to pay particular attention to the general symptoms which at the onset often completely domi-

nate the newly added pathological picture. There occur especially complaints regarding lassitude, general weakness, pain in the limbs, loss of appetite, increased thirst and general malaise, which raise the suspicion of a new affection, the exact diagnosis often being unquestioned to the experienced eye after a few hours. I well remember a case of pernicious anemia affecting a woman aged thirty-four years, in which, erysipelas occurring shortly before death, only produced rise in temperature of from a half to one degree F., giving rise to slight pain in the affected right half of the face, and a scarcely discernible swelling of the wax-like pale skin, which on account of its poor condition of nutrition no longer had the property of reacting to the affection with a local redness, so that the condition could not at once be diagnosticated.

In general the eruption begins with the appearance of one or more closely adjoining, markedly reddened spots, distinctly raised above the level of the skin, which at the onset only produce slight burning and itching. In the development of the erysipelas this sensation increases, giving place to a feeling of troublesome tension, while the process distributes itself further in various directions. The sharply defined border, markedly reddened, and the more or less tense swelling of the hot and often swollen skin, by which it attains a peculiar "lard-like" lustre, is characteristic. From this principal focus various smaller or larger processes advance tongue-like over the healthy skin, so that often an area affected in this manner resembles a map with numerous promontories, bays and recesses. It occasionally occurs that, particularly in a uniform tension of the skin, the round outlines predominate, and that from the principal focus to a certain extent "outposts," insular in form, are sent out into neighboring cutaneous districts at some distance from the chief foci, which are connected by red bands consisting of lymph vessels.

Although the distribution of erysipelas occurs in an apparently arbitrary manner, the nature of the distribution is determined by distinct laws, namely by the structural conditions of the skin, which have been accurately studied by Pfleger. We know, upon the basis of anatomical studies by Langer, that the irregular distribution of erysipelas, its serrated processes, its retractions and protrusions are to be referred to irregular conditions of tension of the skin, whereas in the cutaneous districts in which uniform extensions exist erysipelas mostly shows a diffuse distribution. This knowledge at the same time gives an explanation for the fact that in those areas in which the skin is more firmly adherent to its lower layers by tense connective tissue or adhesions, which place obstructions in the road of the permeation of the erysipelatous process, erysipelas frequently halts and in this manner attains a desirable limitation by these protective measures, being arrested by nature. Thus, it may be explained, that, for example, the chin, which adheres quite tightly to its lower layers, and the upper part of the neck usually remain free, and that the disease rarely extends over the projecting crest of the ilium and over Poupart's ligament.

According to the varying intensity of erysipelas and also according to its location, the erysipelatous inflammation of the affected skin shows a varying picture. We either note, thus particularly upon the skin of the head, a *uniform marked infiltration* which may be determined in these areas better by palpation than by inspection, or by *inflammatory edema*, particularly in those

parts in which the skin is connected with its bony substructure by a thicker layer of fat. A clear example of this is shown by the condition of the eyelids, which in severe cases stand out as semiglobular prominences, often rendering the face unrecognizable. The same observation may be made in regard to the features, upon the scrotum, and, particularly in women that have borne children, in the labia majora which then stand out from the vagina as two large lateral tumors, and in some cases especially when the lymph passages are implicated in the process, almost take on a swelling resembling *elephantiasis*. Although, naturally, the views of authors differ regarding the question, in how far and at what time the lymph apparatus is implicated in the disease, this much may be looked upon as certain, as is also assumed by Lenhartz in his excellent monograph (Nothnagel's Special Pathology and Therapy, Vol. III, part 3), that a *lymphadenitis*, which, after this abatement of the general inflammatory symptoms rapidly diminishes, is to be looked upon as one of the most regular clinical symptoms of erysipelas. The erysipelatous cutaneous inflammation in the majority of cases reaches its acme in from two to three days; then the manifestations in that area which was first attacked begin to decline, sometimes with a lamellar desquamation of the upper cutaneous layers, and the skin becomes pale, whereas the area of demarcation advances a few centimetres. If we are dealing with simple erysipelas which has only attacked the face and the head, the *duration of the affection* will scarcely be longer than eight to nine days, this depending in the main upon the rapidity of the distribution of the process; if, on the other hand, we are concerned with an erysipelas which shows a tendency to further general distribution, and paroxysmally spreads over the entire body, and even attacking those areas anew which were previously implicated and which have healed, we must be prepared for the fact that the disease may be protracted for several weeks or months. Such a condition is designated as *erysipelas migrans or ambulans*, *wandering erysipelas*, and we differentiate further, besides common erysipelas, an *erysipelas vesiculosum seu miliare*, i. e., that form of erysipelas which is characterized by small, closely approximated vesicles upon the skin, and an *erysipelas bullosum*, the so-called pock erysipelas, in which the epidermis is raised in large vesicles which are filled either with clear serum or with pus cells or micrococci containing reddish-yellow fluid, and which often show confluence (*erysipelas confluens*), being raised above the lower layers. If these vesicles have begun to heal so that, as the result of drying, scale and crust formation occurs upon the skin, we designate this process as *erysipelas squamosum or crustosum*. More important, however, are those forms in which, as the result of the marked tension due to transudation in the tissue which may lead to a disturbance and arrest of the circulation, destruction and necrosis of the skin occurs, which I recently saw in the eyelids of a patient aged forty-five years, suffering from uremia and severe facial erysipelas; in such cases we speak of *erysipelas gangrænosum*, and of *erysipelas phlegmonosum* or *pustulosum* in those cases in which the erysipelatous process permeates deeply, producing abscesses in the subcutaneous connective tissue. These are forms of the disease which run their course with severe general symptoms: There is complete anorexia and in some cases the taking of nourishment, even with careful administration in smallest amounts, particularly

if vomiting is present, is almost impossible, so that we must resort to artificial nutrition. With this there is a conspicuously intense thirst. The tongue frequently appears dry, fissured or also fuliginous, and sometimes reminds us of the appearance of the tongue that we have learned to recognize in enteric fever. Severe headache which clouds the sensorium and which may lead to marked delirium complicates the picture, and, finally, comatose conditions arise, which almost always usher in the lethal termination.

Regarding the **course of the fever**, it has already been noted that the affection often begins with an abrupt rise of temperature of from 104° F. to 104.9° F., and even reaching 105.8° F. The temperature may remain at this height for several days, falling by crisis or lysis. In general, the accompanying fever has an intermittent or even remittent type, with decided remissions, followed by marked exacerbations. Although the height of the fever is not strictly dependent upon the inflammatory process, so that, for example, in cases with very severe general or local symptoms lower temperatures are met with (100.4° F. to 101.3° F.), for the most part we may alone gain from the febrile curve an opinion regarding the condition of the local process, in that usually we will not err greatly if in the continuance of high temperature we recognize a constant increase of the process, and in a diminution of the temperature a gradual decline of the affection. In erysipelas migrans a new involvement may be concluded from a renewed rise in temperature.

Some authors, Roger, Frickhinger and Leube, have called attention to the fact that erysipelas in some cases runs an afebrile course, an observation which is in contradiction to the statements of Lenhartz, who in his 140 cases always found an increase in temperature, although sometimes only by careful measurements taken every three hours by rectum. Among the 228 cases which were admitted during the ten and a half years of the existence of Koch's barracks, there were only 3 cases (1.32 per cent.) in whom it was certain that no rise in temperature occurred even upon taking rectal temperatures. It therefore appears that a completely afebrile course in erysipelas belongs to the greatest rarities.

ERYSIPELAS OF THE MUCOUS MEMBRANES

Erysipelas of the mucous membranes is of particular importance, which sometimes in the form of *erysipelas puerperale grave internum* leads to the severest symptoms and subsequent conditions and often precedes cutaneous erysipelas. Thus, we know that erysipelatous angina and coryza which begin with severe chill and high rises in temperature almost always introduce the clinical picture of cutaneous erysipelas even although the affection in itself is characterized less by the immediate prominent local symptoms than by its resulting conditions, in particular secondary facial erysipelas. As the principal point of origin for the mucous membrane exanthem we must look upon the alæ nasæ and the nasal openings. The cases described by St. Philipp, Lennander and Lenhartz which occurred as the results of an entrance to the nasal canal as well as by the internal or external ear, are proofs of the many ways in which the transmission of erysipelas may occur and are certainly of great interest, but have scarcely reached great practical importance. How-

ever, the conditions differ as soon as the *larynx* either primarily, or, as is more frequent, by implication from the pharynx, becomes secondarily affected, as this affection which is characterized by severe difficulty of deglutition and swelling of the lymph glands, as well as by a chill introducing the fever and lasting from one to three days, in a very brief time may produce such dangerous symptoms of dyspnea and laryngeal stenosis that death by suffocation can only be averted by means of an early tracheotomy. It is, therefore, not strange that by a further extension of the erysipelatous inflammation to the bronchi and the deeper situated respiratory passages, the production of bronchitis and circumscribed bronchopneumonic foci may occur, from which, according to Mosny, the cultivation and isolation of a streptococcus has been successful, which in the ear of the rabbit was capable of producing true erysipelas. These pneumonias, by their tendency to occur bilaterally, their slow development of hepatization, and by a marked splenic tumor, are so well characterized that N. Friedreich has particularly designated them as "erysipelatous pneumonias."

Of more importance and of greater clinical interest among these comparatively rare processes is the connection between *puerperal sepsis*, and *erysipelas*, which reaches its severest expression in the form of *erysipelas puerperale grave internum* (Virchow). It is obvious that the woman recently delivered is very readily exposed to the entrance into her body of streptococci, as the external injuries of the labor which have remained are suitable ports of entrance for the invasion of microorganisms. It is then not remarkable that, particularly in the pre-antiseptic period, this form of erysipelas, in consequence of transmission by means of physicians and nurses, was more frequently observed, whereas to-day, with a strict isolation of erysipelas patients, as well as by the rational conduct of labor and the puerperal period, the affection occurs but very rarely. The disease itself, as a rule, begins with a chill, and after lasting from two to three days, with continued fever, may be recognized by a sharply defined margin upon the uniformly reddened and swollen vulva, from which then in the form of an erythema this usually painful inflammation distributes itself upon the back and abdomen as well as over the lower extremities. In a case occurring in Koch's barracks, in a woman aged twenty-five years, who was delivered in her dwelling by a midwife, immediately *post partum* an erysipelas developed in the region of the vulva, the inflammation advanced through the markedly dilated and loosened walls of the uterus and tubes, as was recognized at the autopsy, to the visceral layer of the peritoneum and had produced there the signs of a severe diffuse fatal peritonitis, after three days, with profuse miliary abscesses of the peritoneum, from which streptococci were grown in pure culture, and in the ear of the rabbit constantly produced typical erysipelas.

ACCOMPANYING SYMPTOMS AND COMPLICATIONS

In briefly discussing the complications of erysipelas, the cerebral disturbances which depend upon the principal localization of the erysipelatous process in the face and in the skin of the head are prominent symptoms. They are particularly intense; headache which appears with great regularity, unrest,

implication of the sensorium, stupor and in severe cases marked delirium, which take on a life-threatening character, changing into coma; this I have seen twice, once in an alcoholic aged twenty-five years, and once in a weak, hysterical girl of fifteen years, with the gradual disappearance of the cardiac power causing death. Although these processes which are due to the severity of the erysipelatous affection are comparatively rare, these cerebral disturbances in the form of severe delirium, which directly cause death and which may be due to a complicating meningitis, but which, however, in our cases could be excluded by the autopsy, have been noted with certainty by various authors, thus, for example, in some cases in Leyden's clinic. As the result of the propagation of the erysipelas from the external ear, an *otitis media* may develop, the appearance of which again includes the danger of a meningitis, this being a fact which is based upon anatomical conditions. In this manner suppuration in the *frontal bones and in the antrum of Highmore*, requires operative interference; it has been observed as the result of erysipelas of the pharynx or of the nose. It may be further mentioned that the production of subcutaneous and phlegmonous abscesses, purulent lymphadenitis, and of internal suppuration (*gonitis purulenta*, Hoffa), as well as distributed *cutaneous gangrene*, particularly developing around bedsores, have been observed as occurring in connection with cutaneous erysipelas. Of the changes arising in the organs in the course of the disease, the lobular pneumonias due to aspiration are of the greatest importance, occurring, however, only in the severer cases, with marked disturbances of consciousness, which, further on, may be complicated with endocarditis with succeeding pericarditis. Nephritis is rare; however, slight albuminuria is quite common. Ehrlich's diazo-reaction, to the clinical importance of which M. Michaelis has again recently called the attention of physicians, is well developed, particularly in severe cases.

Erysipelas is a disease which differs from other infectious diseases in its great tendency to **relapses**. We find an explanation for this phenomenon in the fact that by a single recovery from erysipelas, for example, in contrast to scarlet fever or cholera, no immunity is acquired. Although inoculation experiments carried on by Fehleisen at the onset appeared to allow of the conclusion that by recovery from the disease an immunity, although a brief one, was secured, there can now be no doubt that patients who have once been attacked by erysipelas readily acquire the disease again. Experience teaches that some individuals, often for many successive years, usually in spring or in autumn, are attacked by head or face erysipelas, and only then are spared after another affection which has an etiological connection with erysipelas, such as *ozena*, a tear-duct affection, or after an *otitis media* has been completely cured. The designation of so-called *habitual erysipelas* is derived from this, in which often the same sharply limited cutaneous areas are again implicated as in a previous attack. Besides these relapses which, in a stricter sense, affect the same individual after months or years, we differentiate clinically the *relapses* which occur after the first attack, after an afebrile interval of twenty-four to forty-eight hours, appearing with high temperature and with the eruption of a characteristic exanthem, which may repeat itself several times—according to the reports of Hirtz and Widai, in

one case twenty times during three months. An observation of our own regarding the occurrence of the so-called *catamenial erysipelas* (Massalongo) concerns a girl aged twenty-four years, who seven times in the course of twelve months was attacked at the onset of the menses by a fever with a temperature range of 101.3° F. or 102.2° F., with the eruption of a facial erysipelas affecting the right side of the nose, which remained about six days, up to the cessation of the menses. These cases are probably to be looked upon as analogous to those attacks of hemoptysis occurring at the time of menstruation in tubercular subjects. According to reports of v. Leyden and Renvers, Lenhartz and others, these recrudescences are far rarer than the relapses, which, among the country population, are favored by the frequently observed crural ulcer, which then not infrequently, especially in corpulent women, leads to elephantiasis of the lower extremities and the labia.

A few words regarding **erysipelas of the new-born and nurslings**. This is a disease which has become much rarer since the diminution of cases of puerperal sepsis, which was the main source of infection for this form of the disease. Fortunately there is not a great susceptibility to acquire it. Nevertheless, even lately, cases of puerperal erysipelas have become known in connection with ritual circumcision and after unclean vaccination. In the new-born, in the same manner as tetanus, the disease takes its origin from the navel or from the buttock, as well as from abrasions in the face, and then, with symptoms of fever, may distribute itself over the entire surface of the body and may lead to cutaneous necrosis in the same characteristic manner as in an adult.

SECONDARY ERYSIPELAS

Up to this time we have been concerned with erysipelas as a substantive and primary affection, which is by far the more important form of the disease. But we must not neglect the clinical, especially the prognostic importance of secondary erysipelas, which occurs in connection with severe chronic diseases, as acute tuberculosis, or which we have observed in mild endocarditis or arteriosclerosis, in which it may be the direct cause of death.

I remember distinctly a case of a thirty-year-old strong convalescent of enteric fever, in whom, in connection with the enteric fever, in spite of all care, an unusually severe head and face erysipelas occurred as the result of a fistulous opening in the jaw, this existing for two months and finally terminating in death.

This complication with erysipelas, with poor nutrition of the skin, particularly in patients with bed-sores and necroses of the coccyx, favors the accumulation and distribution of further pathogenic agents, by offering a favorable field for them, and is prognostically an unfavorable newly added element.

DIAGNOSIS

As a rule, the **diagnosis** of cutaneous erysipelas offers no difficulties as soon as the affection appears upon the skin. The usually painful area attacked by erysipelas is hot, of a rose-red color, is covered by vesicles, shows an edematous swelling and is sharply separated from the healthy tissues by

an abrupt line of demarcation. The affection usually takes its point of origin from quite insignificant lesions of the skin or from an opening of one of the cavities of the body and it is characterized by a tendency to rapidly distribute itself upon the surface. Regular accompanying phenomena are formed by decided fever (102.2° to 104° F. and over) with marked gastric symptoms, as well as by swelling of the neighboring lymph glands; often there are added to this, albuminuria, slight enlargement of the spleen and endocardial murmurs, which disappear after the disease has run its course; after resolution erysipelas rapidly terminates with desquamation.

But in spite of this distinctly developed symptom-complex which we meet with in erysipelas, the disease may be confounded with other affections which show a certain similarity to erysipelas. In a differentio-diagnostic respect, *simple erythema* must be regarded, which depends upon a transitory hyperemia of the skin, but which runs its course without decided pain or swelling and without a marked rise in temperature; *erythema exsudativum multiforme*, the efflorescences of which, often with a simultaneous existence of severe general symptoms (fever, cardiac murmurs) are constantly limited and show no tendency to further distribution must also be considered. In contrast to erysipelas, *urticaria*, which is characterized by a peculiar itching, as well as by a blotchy eruption and acute superficial lymphangitis, also runs its course with redness, painfulness of the skin and a temperature and is characterized as a substantive affection by its streaked or flaky redness. On the other hand, the definite differentiation between erysipelas and diffuse *phlegmonous inflammation*, which is frequently described as erysipelas and which is characterized by inflammation and redness, may readily give rise to confusions and mistakes in diagnosis. Worthy of note in avoiding this, is the fact that in these diffuse inflammations the redness is of a much darker shade than in the case of erysipelas, and is not limited in any direction, and that further on a hard board-like swelling of the skin exists at the same time, this usually terminating in abscess formation. *Pemphigus* may be differentiated from erysipelas bullosum by the stabile inflammation which runs its course without edematous swelling and constant implication of the lymph channels, and by its more or less local inflammation. Finally, *malignant pustule (anthrax)*, which appears upon the nose or behind the ear, may in rare cases give rise to diagnostic difficulties; this shows a very coarse tumor and is sufficiently well characterized by its indented, excoriated centre; if doubts exist, the microscopic picture and culture experiments will decide the diagnosis.

In this connection I must briefly consider a clinical picture which sometimes gives rise to confusion with true erysipelas, namely, *zoonotic (finger-) erysipeloid*, first described by Fr. J. Rosenbach, which particularly occurs in persons whose occupations require the handling of meat, game and poultry or who work in slaughter-houses or tanneries and the like. We, therefore, observe this disease particularly in the fingers of restaurant keepers, butchers and cooks, as they more than other people particularly come in contact with animal substances. The inflammation, which usually originates in the terminal phalanges, is characterized by a dark red, almost bluish swelling, which, with its sharp border, advances very slowly, so that it only reaches the metacarpus about eight days after its appearance at the tip of the finger. The

general condition of the patients is usually undisturbed with the exception of an unpleasant itching and burning in the affected areas; it is an important fact that a rise in temperature is not observed in this disease. As erysipeloid also occurs in the face, and here usually attains a butterfly-like distribution upon one cheek, very rarely upon both, it is quite possible that, as emphasized by Lenhartz, a large number of these affections, on account of their complete afebrile course, have been looked upon as true erysipelas and described as afebrile erysipelas.

The *diagnosis of erysipelas of the mucous membranes* is connected with great difficulties, and we may state that in case the skin is not implicated in the erysipelatous inflammation a diagnosis cannot be made with certainty regarding the erysipelatous character of the process from the general symptoms, albuminuria, rise in temperature, swelling of the glands, and enlargement of the spleen, these conditions also occurring in every severe inflammation of the throat.

PATHOLOGY

In a pathologico-anatomical sense we understand an acute inflammation due to a streptococcus that enters the skin by means of small lesions, which increases in the lymph-vessel system and advancing from here enters the neighboring tissues. According to the investigations of Volkmann and Steudener, the anatomical alterations in erysipelas not only consist in a hyperemia and in edematous saturation but also in a very decided, more or less dense, small cellular, serous, occasionally, also fibrinous infiltration of the cutis and the subcutaneous connective tissue. According to the localization of the process in the cutis or in the subcutaneous tissue, the changes in one or the other part predominate. In the course of the reddened area, *intra vitam*, we find in microscopic sections, inside of the skin and in the subcutaneous tissue, numerous cocci vegetations, which usually fill the lymph vessels and perivascular spaces and in a particularly plentiful development also the lymph spaces and lymph canals of the skin, whereas the capillaries are always free. At the height of the disease the tissue fibres of the more or less decidedly swollen cutis are separated by the transudating fluid. The lymph spaces occupied by the micrococci are surrounded by a small-cell infiltration and along the external walls of the markedly dilated cutis vessels we often meet a large number of emigrated leukocytes arranged in beautiful rows. On the other side of the limiting red wall the cocci proliferation, as well as the small-cell infiltration has considerably diminished in intensity, and about two to three centimetres on the other side of the inflammatory border nothing more of these changes can be discerned.

We may differentiate three zones: A zone of beginning cocci immigration, which is not characterized externally by any other phenomena, then a zone limited by a red line of demarcation of the inflammatory cell reaction and, finally, a third one with deep-reaching and gradually disappearing cocci vegetations. If the retardation of the process is characterized by an amelioration and decline and swelling of the skin, then the small-cell infiltration is almost entirely over, a process which is removed partly by a granular decomposition partly by resorption in the lymph vessels which are later on tensely filled.

Then by an unusually marked infiltration, *gangrene* may occur, as we have sometimes noted in cachectics.

The vesicle formation in erysipelas occurs in the manner that the cells of the rete Malpighii swell, and that the upper layers of the epidermis, the so-called stratum corneum, by the formation of cavities which are filled by an exudative fluid rich in cells, are raised according to the distribution of the process.

Post mortem, among the general changes of the organs, in which many thrombi of streptococci can be shown, there is almost always a flaccid splenic tumor, which we meet with in almost all acute infectious diseases, particularly in sepsis. Not rarely there is also parenchymatous swelling of the heart muscle, kidney, liver, and muscles of the body, frequently endocarditis and endarteritis, inflammation of the serous membranes and, finally, acute edema of the brain and lungs, which have arisen *sub finem vitae*.

PROGNOSIS

In the main, in pure uncomplicated cases, the prognosis is favorable, although the disease in itself, particularly in erysipelas migrans, as the result of the damage to the organs, and toxic action on the organism, with decrease of cardiac power, and with well characterized signs of collapse, even in young individuals having good resistance, may be the immediate cause of death. The danger of an unfavorable termination is markedly increased if erysipelas occurs as a secondary affection or as a sequel in an enteric fever patient, who, having his powers already weakened by a prolonged illness, can no longer resist the new attack; often in such cases the end is due to a deglutition pneumonia, as the result of unconsciousness. The prognosis is unfavorable in the new-born, and in children in the first month of life, these almost regularly dying; also the prognosis is exceedingly grave if the erysipelas primarily attacks the larynx (laryngeal stenosis!), or when the disease attacks the lying-in woman, because the transference of the erysipelas cocci to the mucous membrane of the genital apparatus gives a possibility of its entrance into the circulation, and of the development of an almost always fatal sepsis.

The average mortality observed in erysipelas, which, however, on account of its decided statistical variation, has no decided value, is given in literature as from 0.85 per cent.¹ to 11 per cent. (Zülzer).²

Before describing the prophylaxis and therapy of erysipelas, a few words are in place regarding the endeavors to utilize the **artificial transmission of this disease for therapeutic purposes**. It was particularly by French authors that these reports were taken up, which dated from the seventeenth century, according to which erysipelas occasionally enfolded a curative action in a peculiar manner; they instituted further observations regarding this condition and finally referred to an érysipèle salulaire or médical. In fact, we know quite a number of diseases in which an accidental erysipelas has brought

¹ Sanitätsbericht der königl. preussischen Armee über die Jahre 1890–1892.

² Erysipelas, *Ziemssen's Handbuch der speciellen Pathologie und Therapie*, Bd. ii.

about a favorable action. Thus, we know from the reports of authors of reputation, that, besides some neuralgias, eruptive diseases of various kinds, scrofulous glandular enlargements, chronic arthritis and similar conditions, also malignant neoplasms have run a favorable course under the influence of erysipelas. Permanent cures of lupus nodules have been described by Cazenave, Bazin, Grivet and Hebra, and, according to a report by Sabatier, an erysipelas accidentally occurring in syphilis causes the symptoms of this disease to disappear more easily than all other methods. However, the idea of practically utilizing these accidental observations for the cure of diseases, by a production of erysipelas, was first made by Després, and particularly by Ricord, who observed the rapid cicatrization of a syphilitic chancre from the effect of erysipelas.

W. Busch was the first in Germany to attempt the cure of malignant tumors by inoculation of erysipelas, and he attained quite remarkable results. After Busch had observed in a woman aged forty-three years, who had upon her nose, forehead and eyes numerous firm sarcomata varying in size up to a pigeon egg, that by the development of an erysipelas, as the result of extirpation of these parts, all the tumors disappeared, he proceeded to inoculate a patient of nineteen years of age, suffering from inoperable lymphosarcoma of the glands of the neck. He placed her in the corner of a ward "in which a patient with an open wound had never been placed without a wound infection appearing." It was shown that, corresponding to the development of the erysipelas, there was a retardation and even a complete disappearance of the tumor masses at the end of the first two weeks, which, however, with the disappearance of the erysipelas, reappeared so that a permanent cure did not result.

Since Fehleisen's discovery of the streptococcus erysipelatos, the process of transmission is considerably simplified, for now, as was carried on successfully by Fehleisen himself, a pure culture of the micrococci is injected into the neighborhood of the tumor or even directly into the tissue of the tumor. Here a comprehensive work by W. B. Coley requires mention, who reports partly very remarkable results in the treatment of 38 malignant tumors by means of artificial infection.

An explanation for these, in many cases curative processes, is found in the pathologico-anatomical investigations which have been carried on by Rindfleisch, Neisser and Neelsen. In the microscopic picture, in place of the sarcoma cells Rindfleisch was able to recognize a rapid beginning resorption, a fatty metamorphosis of the cellular elements, to which he referred the disappearance of the tumor and Neisser observed that the cocci had directly entered the carcinomatous tissues completely surrounding the cancerous masses, producing a mucus "decomposition" of the epithelial cells.

Nevertheless, in the course of time, because of the uncertainty of success, and particularly owing to the danger in every case of erysipelas, and because of death occurring from artificially induced erysipelas, there has been a cessation of experiments in this direction, also because some authors, particularly Petruschky, noted no retardation of the carcinomatous nodes, but a decided diminution in the strength of the patient.

TREATMENT

Special attention must be devoted to the **prophylaxis** of erysipelas, which must be considered as especially important. In the first place we know from clinical experience that not only those suffering from erysipelas, but also those convalescing from the disease are still capable of transmitting erysipelas; besides we have learned from the investigations, of v. Eiselsberg, Emmerich, and others, that the streptococcus which produces erysipelas may retain its property of life and virulence for a long time even outside of the human organism, and we know from the numerous observed hospital epidemics that this microorganism remains in hospital wards for a long time and thus very readily attacks weakened individuals. To this must be added that recovery from erysipelas does not confer immunity and, although the liability to contract erysipelas is not particularly distributed, the disease may attack any one regardless of age or sex. Further, it is to be noted that some persons have an increased predisposition to erysipelas. We have already noted that individuals with large open wounds, with bed-sores, fissures and excoriations, are particularly in danger, and we know that even a slight lesion of the mucous membrane is sufficient to permit the entrance of streptococci, which, according to C. Gerhardt, localize with special preference in the tonsils. Further Küster has called attention to the fact that an infection may even occur through the tender epidermis of newly-formed cicatrices.

Under these circumstances, it is quite clear that the surgeons whose patients were particularly exposed to the danger of infection, combated erysipelas with all the means at their command, and it is a grand triumph which the antiseptic treatment of wounds has attained that, after the introduction of this method, as is shown by the statistics of Küster and others, the percentage of cases of erysipelas has been greatly diminished, thus, for example, in the Augusta Hospital in Berlin, in the years 1871 to 1885, it has fallen from 7 per cent. to 0.74 per cent. We must, therefore, endeavor to perform all operations away from the neighborhood of erysipelas cases, and a strict isolation of these patients must be looked upon as an absolute necessity in surgical hospitals which nowadays are mostly overfilled. Although the carrying out of a strict isolation of erysipelas patients in the divisions of the medical hospital is combined with great difficulties, an attempt should be made to isolate the erysipelas cases from other internal diseases in order to prevent a transmission of the affection. That the puerperia and the new born are to be protected from every contact or from the neighborhood of erysipelas patients has already been mentioned. If we wish to be successful in preventing the numerous relapses of erysipelas we must carry out a careful bodily examination, particularly of the nose, ears and eyes (tear-duct affection!) and eventually treat these affections; we must eliminate the primary disease and thus remove the source of infection. Also, in recrudescing and relapsing erysipelas, which after short pauses after recovery always return, a disinfection of the living-rooms is to be carried out, as it is not unlikely that the relapses are due to the germs which remain in the dwelling.

General Therapy.—Regarding the therapy of erysipelas, apart from serum treatment, the application of which shall concern us later on, we may differentiate between a *local* and a *general treatment*.

To begin with the oldest measures, which now have been generally abandoned and only retain a historical interest, Hüter's method, the subcutaneous injection of 1 to 2 cc. of a 2 per cent. carbolic acid solution at the border of the erysipelalous area, for a long time maintained general recognition. Particularly if the injections were carried on at some distance from the diseased cutaneous area, according to the investigations of Aufrecht, Nippold and others, a further implication of the inflamed boundary was hindered and improvement in the general condition took place. Until about twelve years ago this method was still warmly recommended by v. Nussbaum and Rosenthal, who combined it in a successful manner with the so-called Pirogoff camphor cure, till gradually the process gave way to the method introduced by Küster, the injection of a 1 to 1,000 corrosive sublimate solution at the border of the erysipelalous area or close to it. Starting with the same idea as these authors, namely to limit the course of erysipelas at the point of entrance of the organism, or at least to inhibit its further distribution, Kraske advised, after a thorough cleansing of the diseased cutaneous area, to carry out numerous punctiform scarifications or incisions, up to 1 cm. in length, these reaching 1 to 2 cm. beyond the advancing border, and after thoroughly squeezing these parts to apply a 5 per cent. solution of carbolic acid as well as having a 2½ per cent. carbolic acid dressing. Kraske's method, which was modified by Riedel, and particularly by Gluck, who applied a 60 per cent. ichthyol salve or solution in every cut, did not permanently retain adherents, and it is a fact that the use of the method in erysipelas of the head was not advised by the discoverers themselves.

On the other hand, remedies that acted *mechanically*, such as those first proposed by Wölfler, and which were certainly harmless, seemed worthy of a further observation and trial. Wölfler proceeded in the manner that at some distance from the border of the erysipelas a piece of plaster about the breadth of the thumb was tightly applied, and, where the anatomical conditions permitted, it was applied in a ring form, which was only taken off four days after defervescence, with a view to limiting the transmission of the streptococci in the lymph tracts in this manner. By the aid of this method, in which Wölfler observed a limitation of the process in head and face erysipelas, no favorable results were obtained by other observers, as, for example, by Lenhartz and Vierordt, for, as we also can state, no decided influence upon the propagation of the process could be noted. On the other hand, especially in a skin easily irritated, formation of eczema occurs. Wölfler's process was modified further by Buch, and particularly by Kroell, in that this author used an elastic bandage, which was also used upon the head to prevent the distribution of facial erysipelas, this being in the form of a moderately tight band, applied around the forehead. In place of the adhesive strip compression, P. Niehaus advised painting with collodium to localize the process. As the experiences did not lead to the desired results, it was attempted to immediately inhibit the development of the infectious agent by limiting the passage of air from the erysipelalous cutaneous areas. This was attempted

by the use of oil colors (Barwell), traumaticin, further, according to the proposition by Otto, by the use of a solution of 2 parts of wax and 20 parts of siccative in 100 parts linseed oil, and, besides, by pasting over guttapercha paper (Kolaczek).

In our opinion, still greater therapeutic value than these procedures, the use of which, in spite of all praise is questionable, is obtained from the use of ichthyol, which may be used in a 10 per cent. to 50 per cent. collodium mixture, or as ammonium sulpho-ichthyollate with vaselin (1:3 or 1:1), in a quite thick layer, over the 2:3 cm. of the healthy as well as over the erysipelalous cutaneous area. Although we cannot speak of a specific curative effect of this remedy, excellent results have been reported from the use of this medicament by many, Nussbaum among others, who refers the favorable action of the ichthyol to its "reducing action"; he states that "this cripples the soil so that the cocci are not capable of increasing, and, therefore, are prevented from manifesting their pathogenic action." These favorable reports have received a decided support by Klein, and, particularly upon the basis of a large experience, by Fessler. Regarding our own experiences, we can only say that the ichthyol which was used in the Institute, in the division for infectious diseases, in a solution of ichthyol 10.0 in glycerin 90.0, has lately been employed as ichthyol vasogen (10:90) in large amounts, as well in erysipelas as in eczema, and in abscesses with furunculosis; its action has been favorable, particularly if two inunctions were applied per day, respectively packings (thick layer of ichthyol and a light cotton bandage), and not stopped too soon but even kept up for some time after a complete cure. In fact, the previous, markedly tense, swollen and glistening skin after a few days shows folds; palpation which produced pain in the local area prior to the ichthyol therapy no longer causes this, and all irritative phenomena decidedly ameliorate or markedly improve.

Besides ichthyol, which possesses an inhibiting action to the growth of cocci, other remedies, particularly the *strong antiseptics*, are of use, without our being able to mention them all. Thus, salves of varied composition and in manifold concentration, as for example, a 1:1,000 sublimate vaselin (Gottstein), a 5 per cent. carbolized vaselin (Rosenbach), a mixture of creolin-iodoform-lanolin (1:4:10) after Koch, a 10 per cent. carbolized oil after Konetschke, which is applied partly to the erysipelalous area and to some little distance beyond in the healthy surroundings, are of value. Hofmokl, further, has used 3 per cent. to 5 per cent., in children 2 per cent. to 3 per cent., carbolized compresses, excluding the air, and Amici has used repeated applications every two hours to the erysipelalous skin of carbolic acid and alcohol in equal parts, in a sensitive skin carbolic acid and glycerin in equal parts, as well as a 1 per cent. corrosive sublimate-glycerin solution. Further, two to three times daily for one minute a 1 per cent. ethereal corrosive sublimate solution is used (corrosive sublimate, citric acid 1.0, absolute alcohol 5.0, sulphuric ether add 100.0) according to the process of Cayet and Talamon, followed by boric acid applications, apparently with very favorable results upon the affected areas. Again, Fraipont has advised applications of a thin sublimate solution, and Schwimmer has employed a 30 per cent. to 50 per cent. resorcin-glycerin solution. In connection with this, the treat-

ment of the erysipelatous, that is, adjoining, skin, with purified turpentine oil, which Lücke previously cleansed with ether or alcohol, which is painted from the normal to the diseased zone, and, further, the method used by Hamburger with good success, inunction once or twice daily of a tincture of iodine, 2 to 3 centimetres beyond the area of the disease, particularly, however, the local use of absolute alcohol, in the form of frequently repeated washings (Behrend) or linen compresses with a protective covering (v. Langsdorff), require special mention.

[MacLennan has recently called attention to the use of a saturated solution of picric acid in the local treatment of erysipelas. He finds that it arrests the spread of the cutaneous lesion and relieves the pain and burning better than carbolic acid, inert powders or ichthyol. Fothergill also speaks favorably of the local use of a saturated solution of picric acid in erysipelas.—Ed.]

The general treatment in erysipelas has for its chief object the maintenance of the undiminished power of the heart. If only transitory irregularities in the pulse beat or in the pulse tracings are found, small doses of digitalis are in place and we administer, of the solution: infusion of digitalis 0.5 in 200.0 with the addition of 0.5 or 1.0 tincture of strophanthus to increase the rapidity of the action, and by the addition of the same amount of hydrochloric acid, as fever patients with gastric disturbance bear digitalis more readily in this mixture and vomiting is avoided; every two hours a tablespoonful is taken so that daily 0.25 grams of digitalis are administered. It is rare that this remedy must be continued for longer than four or five days and I do not believe it advisable to give more than the total dose of 2 grams of digitalis. If the use of heart tonics is indicated for a longer time it is advisable to give a caffein solution (sodio-benzoate of caffein 0.5 to 1.0 per day) or four to five times daily a benzoate of camphor powder (acid benzoic camph. trita 0.1). In especially severe cases three should be frequently repeated injections of camphor (camphor 1.0, ether 5.0), in spite of the great pain which is caused by the action it must be continued and the injection should not be withheld too long.

A symptom which is particularly troublesome to the erysipelas patient is the *severe headache*, which is best combated by an ice bag, or if this cannot be used on account of the restless condition of the patient, ice-water applications can be used.

The question now arises regarding the advisability of employing *antipyretics*: in the first place to combat the general symptoms, particularly the cephalalgia, and occasionally to diminish the very high fever. In general, we believe it advisable to limit the use of these remedies on account of their threatening secondary action upon the heart. This is also the reason why A. Baginsky¹ and others warned against a forced use of antipyretics and simultaneously advised the use of heart tonics if antifebrile remedies are administered. If we intend to bring down the temperature to quiet the patient, especially if he has been for a long time bed-ridden, the organism having been weakened, in employing antipyretics the palliative value of which

¹ Die Antipyrese im Kindesalter. Berlin, 1901.

can by no means be denied, the simultaneous use of heart tonics is advised at the same time. Of greater value, however, especially if marked unrest, insomnia and disquiet are present, according to Lenhartz, are luke-warm baths of five to ten minutes duration, given two to three times daily, followed by cold affusions which act strongly upon the skin, thus preventing the formation of bedsores, but particularly acting upon the sensorium which is so often the cause of a lethally terminating deglutition pneumonia. It is also necessary to pay attention to the digestive tract, this is best done by the use of castor oil, enemata of glycerin or clysters. In the administration of calomel (gargling with potassium chlorate!) care is enjoined, as not infrequently marked intoxication phenomena appear (gingivitis, stomatitis, salivation, loosening of the teeth and the like) which not rarely last for weeks. If it is desirable to employ internal medication, weak acid mixtures should be given, hydrochloric or phosphoric acids, wine of pepsin and the like. Diuresis should be favored by the administration of cold water and lemonade (1 to 1.5 litres of urine per day). In the fever stage solid food should be avoided, milk, bouillon, meat broths, and the like should be employed. In severe cases it is advisable to give some form of alcohol in moderate amounts as a stimulant and heart tonic, as the experiences which have been gained by the alcohol therapy in medical clinics, as well as in gynecological clinics (Ahlfeld, M. Runge and others), in puerperal sepsis due to streptococcus invasion, have furnished us such favorable results that we should not like to forego the use of this auxiliary remedy. When in the course of erysipelas, hallucinations, delirium and jactitation and similar conditions occur, chloral hydrate by mouth (1 to 2 grams), or by suppository (2 to 3 grams) is advisable. If the remedy is vomited or is not well borne, it will be necessary to use hypodermics of morphia; with this, however, it is necessary to control the action of this remedy on the organism after the first injection, as, even after small doses, unpleasant resulting conditions, attacks of vertigo, and mild symptoms of collapse have been observed. For this reason, at the onset, in determining the dose of morphia for the night it is necessary to be particularly careful as the physician rarely has an opportunity for observing the condition of his patients during the time when the drug is acting. Regarding the treatment of the various complications occurring in erysipelas, it is only necessary to say that they are to be treated upon general principles.

Antistreptococcic Serum.—In conclusion, the use of antistreptococcic serum is to be mentioned, which was obtained by Marmorek in Pasteur's Institute by the use of highly virulent streptococci. In spite of the fact that Chantemesse, in 501 patients, was able to observe that the local process after the use of this remedy is shortened, that sometimes even after twenty-four hours a decrease in the swelling, redness, and painfulness was observed, and that the general condition, often even after a few hours after an injection of 20 to 40 cc., showed a conspicuous improvement, particularly the temperature declining, other observers, for example, Bolognesi and Roger have pointed to the fact that equally favorable effects are also attained by simpler measures and that the results cannot by any means always be referred to the serum treatment. The experiences which have been gathered in the division for infectious diseases in Petruschky's Institute with the Marmorek serum do not.

appear to justify us in ascribing to the serum an influence which is worthy of mention. The observations of Lenhartz teach that neither a diminution of the temperature nor an improvement of the general condition nor of the erysipelatos process could be observed. Nevertheless, the endeavors to obtain a serum which decreases or destroys the pathogenic action of the streptococcus have not been given up. Of primary importance for such a serum is the fact that a positive serum is only active against *certain varieties* of streptococci, and we must assume that it only acts against the streptococcus variety from which it is obtained, and does not convey protection against other forms of streptococci. In the proper recognition of this condition, Denys and his pupils have immunized animals with various streptococci and have thus obtained a polyvalent and antistreptococcus serum, of the clinico-therapeutic value of which we are at present unable to give an opinion. Nevertheless, I believe that I may say even now that it will be well not to entertain too great hopes regarding this remedy, as, up to the present at least, it has not been possible to simultaneously immunize animals against all varieties of streptococci and as the previously used sera have been produced by the aid of animal pathogenic streptococci which, according to the investigations of Petruschky, and to later investigations, are not pathogenic in man. We know now, from the investigations of Neufeld, that even the blood of a human being who has recovered from a streptococcus infection was not even able to protect against the streptococcus cultivated from his own blood! For the present, therefore, the outlook for a later success by the production of a polyvalent serum is quite meagre.

Nevertheless, we are entering a new century under very favorable auspices; the past decade has presented us with the noble gift of the diphtheria curative serum, in regard to which, in spite of great opposition, and after laborious trials, the battle has become a recompensing triumphal march through the entire earth and now as one of our greatest therapeutic agents has taken its victorious place in medicine. Bacteriology, and at this time its most noble branch, *immunity investigation*, in which results have been attained in the last years by R. Koch, v. Behring, Ehrlich, Brieger, R. Pfeiffer, A. Wassermann, Metschnikoff, Buchner, Bordet and others, is still laboring to solve the problem of a specific treatment of infectious diseases. What we are to attain in this realm still rests with the future, nevertheless, we venture, even to-day, to express the hope that at a not too distant time it may perhaps be possible, in a similar manner as has already been described by R. Pfeiffer and A. Wassermann in the animal experiment, to produce a serum in the treatment of the sick, which, for example, may make harmless the infection by enteric fever or cholera. Just so, although this appears to be more distant, because the processes are not exclusively confined to one pathogenic agent, the possibility is not excluded that we may succeed in combating erysipelas, especially preventing the clinical course of the sorrowful pathological picture of puerperal sepsis, which is produced by streptococcus invasion, and to-day, in spite of all labor and the utmost care, we are almost in a helpless position when opposed to it. It is possible that in a sero-therapeutic direction we may favorably influence this process and by a specific method of treatment bring about a favorable termination.

EPIDEMIC CEREBROSPINAL MENINGITIS

By H. EICHHORST, ZÜRICH

ETIOLOGY

ABOUT the year 1902 the newspapers of Switzerland reported that in a small area of the Canton Thurgau, epidemic cerebrospinal meningitis had appeared. This disease is not unnecessarily feared and, on account of its regular and prominent phenomena, has received from non-professional persons the name of *epidemic wry-neck* or *epidemic spasm of the neck*.

On account of the ease of communication, it is not at all unlikely that the disease may be spread readily from its point of origin.

If the diseases of the nineteenth century are spoken of, epidemic cerebrospinal meningitis must be prominently mentioned, as, for the first time, at the beginning of the last century, the disease appeared and physicians began to observe it closely and to describe it. It is interesting to note that the western part of Switzerland represents the point of origin of the disease. It was in the spring of 1805 that, in Geneva, an affection occurred which showed an epidemic distribution unknown to physicians up to that time; this disease was epidemic cerebrospinal meningitis. Since that time the disease has slowly spread more and more; especially in the first decades of the last century only very few epidemics were recognized, first in France, and later on also in other countries.

Naturally, the question arose whether we were dealing with an affection unknown up to then, and whether it was an entirely new disease. This is not very likely as we have no grounds to determine that special conditions prevailed which permitted this disease to appear in the year 1805, and that especially favored it. From the descriptions of older medical writers it can be concluded with more or less certainty that the disease existed. Nevertheless it appears from what has been mentioned that it is quite proper to look upon epidemic cerebrospinal meningitis as an affection of the nineteenth century.

Those who desire to follow accurately the epidemic distribution of cerebrospinal meningitis may be referred to the careful and exhaustive compilations which Hirsch has given in his handbook on historico-geographic pathology. There is also a book by Dr. Jaeger (*Cerebrospinal Meningitis as a House Pestilence*, Berlin, 1901), that I would recommend very highly.

Although epidemic cerebrospinal fever occurred for the first time in Switzerland and thus aroused discussion, our country was subsequently spared from this affection. During my professional activity in Switzerland, amounting to about twenty years, with the exception of the previously-mentioned epidemic in Thurgau, I have never heard anything of an epidemic of this disease. By this, I do not desire to infer that during the period mentioned

I have not treated cases of purulent cerebrospinal meningitis. Quite apart from such patients in whom the affection developed following other infectious diseases, such as fibrinous pneumonia, ulcerative endocarditis, purulent otitis media and other diseases as complications, I have seen patients who, independently of any other disease, showed an acute purulent cerebrospinal meningitis; nevertheless, their number only reaches the very modest figure of five. All my patients were of the male sex and between the ages of fifteen and twenty-five. There was no connection between any of these patients, neither regarding locality nor time; years occurred between the individual affections. These patients then suffered from what is usually called *sporadic cerebrospinal meningitis*.

I do not wish to conceal that, especially in one of my patients, I had a suspicion that he might prove to be the starting-point of an epidemic of meningitis. The patient was a strong powerful recruit, and was sent to the medical clinic from the garrison stationed in this city, and died here in a few days of a purulent cerebrospinal inflammation. Now it is well known that this disease is *common among soldiers*, being frequently brought into garrisons by recruits, where it continues for some time; especially in the French and German armies, numerous military epidemics have been described, and in the investigations published by Jaeger it is unquestionable that in the German army this affection has slowly but continuously gained in distribution and extent from year to year.

North America belongs to those countries in which in the last few years among the denser population, widely distributed epidemics have been observed. In Massachusetts, for example during the years 1887 to 1895, there occurred 1,179 deaths from epidemic cerebrospinal meningitis, 608 males and 571 females.¹ In individual North American cities the disease has found its way and attained a foothold and thus has become endemic. To these, for example, belongs Boston, and we have very accurate reports by Critzmann,² Osler,³ Wentworth,⁴ Williams,⁵ especially however, from Councilman,⁶ Mallory and Wright.⁷

On account of the incessant activity of travel by means of ships between the old world and the new there can be no doubt that the affection has been carried from one part of the world to another, and such introduction of the affection has been observed repeatedly. The appearance of many epidemics in individual North German cities and seaports, for example, in Hamburg,

¹ Epidemic cerebrospinal meningitis and its relation to other forms of meningitis. A report of the State Board of Health of Massachusetts. Boston, 1898.

² Critzmann, La méningite cérébro-spinale épidémique. Annal. d'hygiène, 1898, p. 115.

³ W. Osler, The arthritis of cerebro-spinal fever. Boston Med. Journ., 1898, No. 26.—W. Osler, The Cavendish lecture on the etiology and diagnosis of cerebro-spinal fever. Boston Med. Journ., 1899, Nos. 1 and 2.

⁴ A. H. Wentworth, Epidemic cerebrospinal meningitis. Lancet, Oct. 1, 1898.

⁵ F. H. Williams, Seventy-one cases of cerebro-spinal meningitis. Med. and Surg. Rep. of the Boston Hosp., 1898, ix.

⁶ Councilman, Cerebrospinal meningitis. Boston Med. Journ., 1898, No. 7.

⁷ Councilman, Mallory and Wright, Epidemic cerebrospinal meningitis. Amer. Journ., March, 1898.

seems to be in connection with the introduction of the disease from America and just so, the epidemics in Copenhagen, which Faber has reported,¹ appear to be of North American origin.

Up to this time epidemics of cerebrospinal meningitis without exception have characterized themselves by being limited to very small districts. In the epidemics occurring among the military population, the disease usually appears in individual garrisons, and in these only in distinct departments and rooms of the garrisons. If the epidemic prevails in a locality it finds a firm foothold in distinct streets and houses. That large cities or extended country districts have been affected simultaneously to a like degree has not yet been observed. It is noteworthy that an epidemic not rarely affects a small number of persons and is ended within a few weeks. But there are numerous exceptions to this rule. Although epidemics have been observed at all seasons of the year they are by far most frequent in the months of the winter and spring for which fact, up to now, there is no satisfactory explanation.

Epidemic cerebrospinal meningitis is to a prominent degree a *disease of youth*, and quite a number of epidemics have been known that prevailed pre-eminently among children. After the fortieth year of life the disease only occurs very exceptionally.

The *en masse* and epidemic appearance of the malady has from the onset produced the impression among physicians that the disease is of a contagious or *infectious nature*. For this reason it cannot appear strange that in this affection, as in all other infectious diseases, the *pathogenic organism* has been looked for, with a probability almost approaching certainty that this has been recognized in a schizomycete, which we owe to the investigations of Weichselbaum² and especially to Jaeger.³ If on account of its origin epidemic cerebrospinal meningitis must be looked upon as a disease of the nineteenth century, it is especially the bacteriologic investigation regarding its causative agent that has stamped it as modern.

The peculiarity that the pathogenic agent in question is very frequently found inside of cells has led Weichselbaum to give it the name *micrococcus intracellularis meningitidis*. I must admit that in my opinion the designation *meningococcus* is more to the point, and is perhaps preferable on account of its brevity. If some physicians speak of a Weichselbaum-Jaeger meningococcus, I for my part do not object, although I should like to remark that we are gradually being so overwhelmed with a profusion of proper names, that the student of medicine encounters greater and greater mnemonic difficulties, and thus the opportunity for confusion becomes decided and will rapidly increase.

It will be remembered that the founder of bacteriology, Robert Koch, has set up three requirements that a bacterium must possess to be looked upon with absolute certainty as the causative agent of an infectious disease.

¹ Erik E. Faber, Bakteriologische Untersuchungen von Fällen epidemischer Cerebrospinalmeningitis in Kopenhagen im Sommer 1898. Zeitschrift für Hygiene, 1898, Bd. xxiv, Heft ii.

² Weichselbaum, Ueber die Aetiologie der acuten Meningitis cerebrospinalis. Fortschritte der Medicin, 1887, Heft xviii und xix.

³ H. Jaeger, Zur Aetiologie der Meningitis cerebro-spinalis epidemica. Zeitschrift für Hygiene, 1895, Bd. xix.

1. The organism in question must be invariably found present in the infectious disease in question; besides it must be successfully obtained from the products of the disease artificially and in pure culture; and, finally, a transmission of pure culture in animals must give rise to the same anatomical and clinical changes as are peculiar to the infectious disease in man. An investigation of the transmission of the pure cultures to man is naturally excluded.

Have all of these three requirements of Koch been fulfilled regarding the meningococcus? We must not conceal the fact that there are reports from some years back in which in the inflammatory products of the affected cerebral membranes other germs were found. In the last few years, however, the reports correspond more and more in that in epidemic cerebrospinal meningitis the meningococcus has been detected with great regularity. It may be sufficient to mention some authors, of whom only those will be brought forward that have had great experience and unquestionable opportunity to observe epidemic cases of cerebrospinal meningitis. Heubner¹ performed lumbar puncture in 14 patients and was able to determine the meningococcus in 8 cases. Fürbringer² punctured the subarachnoid space of the lumbar cord of 10 cases of cerebrospinal meningitis and found the meningococcus in each case. The same conditions that were recognized in Berlin were also noted in Boston. In 16 lumbar punctures Osler³ found the meningococcus 13, perhaps even 14, times, and upon page 323 of the previously mentioned paper of Councilman, Mallory and Wright, it is reported that among 35 autopsies the meningococcus was only missed twice. Regarding investigations in Denmark, the previously mentioned paper of Faber shows that among 51 lumbar punctures 27 showed the presence of the meningococcus. Pfaundler⁴ found in 7 cases of epidemic cerebrospinal meningitis which he observed in Gratz the meningococcus without exception in the fluid obtained by lumbar puncture.

We are in possession of an even greater number of similar reports in which, however, the investigation deals with smaller statistics. We may mention for example, the researches of A. Fränkel, v. Leyden, and Huber.

The production of *pure cultures of the meningococcus* did not take place without decided difficulties nor was success at first attained in endeavoring to produce the characteristic changes in animals with these pure cultures. Subcutaneous injections of the meningococcus, in contrast to Fränkel's pneumococcus, showed no influence, whereas injections into the peritoneal cavity at least produced inflammatory processes. However, after unsuccessful endeavors with guinea-pigs and rabbits, Heubner succeeded in obtaining positive findings when he injected meningococci into the subarachnoid space of the spinal cord of a goat, an operation that has been called *inverse, more correctly perhaps, retrograding lumbar puncture*. The animal was attacked by purulent

¹ Heubner, Zur Aetiologie und Diagnose der epidemischen Cerebrospinalmeningitis. Deutsche med. Wochenschr., Juli, 1896.—Heubner, Ueber den Meningococcus. Deutsche med. Wochenschr., 1897, Nr. 11.

² Fürbringer, Congress für innere Medicin, 1898.

³ W. Osler, The Cavendish lecture on the etiology and diagnosis of cerebrospinal fever. Boston Med. Journ., 1899, Nos. 1 and 2.

⁴ Pfaundler, Physiologisches, Bakteriologisches und Klinisches über Lumbalpunktion an Kindern. Wien und Leipzig, Verlag. Braumüller, 1899.

meningitis. In Boston the same experiment succeeded as I have learned from the previously mentioned Board of Health Report.

We must be quite clear about the fact that epidemic and purulent meningitis are not the same thing. Even although epidemic cerebrospinal meningitis is of a purulent nature, by no means every purulent inflammation of the cerebral membranes is in meningitis. As we recognize a great number of microorganisms which are capable of producing purulent inflammations, it cannot appear strange that here and there in purulent cerebrospinal meningitis other bacteria and not the meningococcus have been found, especially in those cases in which the purulent meningitis did not belong to the epidemic variety. Under these circumstances in the purulent exudate of the meninges various microorganisms have been met with, among which may be mentioned streptococcus pyogenes, staphylococcus pyogenes, bacterium coli communis, typhoid bacilli, and especially Fränkel's pneumococci. Some very prominent and experienced investigators have especially maintained that the pneumococcus produced epidemic cerebrospinal meningitis. I am of the firm opinion that these reports are due to various errors, as a certain superficial resemblance in shape which exists between meningococci and pneumococci has given rise to mistakes. This does not, however, mean that there is any doubt about pneumococci producing purulent meningitis which, under some circumstances, may even show a certain epidemic distribution. Fränkel¹ himself, the discoverer of the pneumococcus, has described an investigation of cerebrospinal meningitis in which pneumococci were found besides meningococci, in which, therefore, a so-called mixed infection was present.

In fact *mixed infection* in every purulent meningitis, but especially in epidemic cerebrospinal meningitis plays a decided rôle, for besides the previously mentioned pneumococci, especially the streptococcus pyogenes and staphylococcus pyogenes, occasionally influenza bacilli have been found besides meningococci in the exudate of the affected cerebral membranes. For an inexperienced bacteriologic investigator certain difficulties arise with this, for it may easily occur that an inexperienced bacteriologist may confuse staphylococci with meningococci. Besides, occasionally, meningococci also occur as secondary pathogenic agents. True, Heubner² for example, in 14 cases of tubercular meningitis twice found meningococci besides tubercle bacilli.

According to my firm opinion, after continued careful investigation it will be determined as an assured fact that epidemic cerebrospinal meningitis owes its origin to only one pathogenic organism, the meningococcus. In the dispute which is still going on regarding the importance of this microorganism in some professional circles, we are reminded of similar diversity of views which occurred a few years ago regarding the pneumococcus and its original connection with fibrinous pulmonary inflammations. In this case it was also believed that some other microorganism might come into question as the cause of pulmonary inflammation, whereas it was determined with more and more certainty later on that only Fränkel's pneumococcus gives rise to fibrinous pulmonary inflammation.

¹ A. Fränkel, Deutsche med. Wochenschrift, 1896.

² Heubner, Ueber den Meningococcus. Deutsche med. Wochenschr., 1897, Nr. 16.

As in the case of other infectious diseases, there are also individual, or *sporadic cases* of epidemic cerebrospinal meningitis. These may very readily be the points of origin for a larger epidemic if they are not properly recognized and by proper isolation and disinfection rendered harmless to those around.

An opinion regarding an individual case of purulent meningitis, as to whether it belongs to the epidemic form or not, can only be determined with certainty by means of lumbar puncture, and the fluid obtained in this manner being examined for meningococci, and from this it can be seen how great is the importance of the meningococcus in a purely practical respect.

Thus, it is necessary for us to become acquainted as minutely as possible with the *morphological and biological properties of the meningococcus*, and from this we shall add greatly to our practical knowledge.

In epidemic cerebrospinal meningitis meningococci are frequently met with in the cerebrospinal and ventricular fluids, so that by their turbid and flocculent, occasionally almost purulent, appearance, it seems as though a fluid exudate is mixed with them, but also in those purulent infiltrates which traverse the tissues of the pia mater they are often met with. In many cases they are the only microorganisms in the inflammatory area. In other cases mixed infections with pneumococci, Friedländer's bacilli, influenza bacilli, streptococci, and staphylococci have been observed. In individual experiences that have been reported, in which, in spite of definite cases of epidemic cerebrospinal meningitis, no meningococci have been found in the places mentioned, I cannot help thinking that with an increasing familiarity with the meningococcus such observations will become less and less frequent. They will not disappear entirely because meningococci may have been previously present or they may have been forced by other microorganisms to disappear.

The number of meningococci varies greatly. They occur occasionally in such small numbers that it requires prolonged search before even a few are found. Under such circumstances it will be well to follow Huber's¹ experiences and to minutely investigate the fluid of the cerebral ventricles; it should also be noted that the number of meningococci and the severity of the morbid manifestations by no means always are in a regular proportion to each other. Sometimes for a very long period after the onset of the disease meningococci can be determined. Thus, Frohmann² reports that in a case in which defervescence occurred only upon the 295th day of the disease he was still able to determine virulent meningococci in the cerebrospinal fluid upon the 235th day of the disease.

Without doubt—and perhaps not even so rarely—meningococci are carried into other organs by means of the circulation thus producing *specifically metastatic inflammations* in them. In an articular inflammation which developed in the course of a purulent meningitis, Fronz³ and Osler⁴ have found meningococci in the contents of the joints, and in 10 cases of pulmonary

¹ Huber, Deutsche med. Wochenschr., 2 Juli, 1896.

² Frohmann, Deutsche med. Wochenschr., 1899, Nr. 42, p. 257.

³ E. Fronz, Ueber eiterige Gelenkentzündungen im Verlaufe der Meningitis cerebrospinalis epidemica. Wiener klin. Wochenschr., 1897, Nr. 15.

⁴ William Osler, The arthritis of cerebrospinal fever. Boston Med. Journ., 1898, No. 26.

inflammation, Councilman, Mallory and Wright only twice found Fränkel's pneumococci, whereas in the other cases meningococci were found in the inflamed pulmonary portions. Jaeger¹ has demonstrated meningococci in the urine, but they have been looked for in the blood and in the contents of the herpetic vesicles without result by Huber² and Faber,³ whereas Thiercelind and Rosenthal⁴ have found them in the blood.

Of great practical importance is the observation that they are not infrequently met with in the excretions of the nose, the pharynx, and the bronchial mucous membranes and in the exudates from the ear. Naturally, they also occur in the nasal secretions of healthy persons, but, whereas Councilman⁵ in 19 cases of meningitis found them 10 times in the nasal excretions, in 12 other patients they were only found twice.

Now in finding meningococci at the last-mentioned points, it should not be assumed that they have reached these areas from the inflamed meninges, but the thought arises that they may have been borne from the previously mentioned areas to the meningeal spaces by means of the lymph channels or perhaps by the circulation, thus producing cerebrospinal meningeal inflammation. These views may be utilized as preliminary measures in that during the time of epidemics of meningitis healthy persons should be advised to use solutions of disinfectants in the oral and pharyngeal cavities after meals and to use nasal douches mornings and evenings.

Now what induces meningococci which previously have remained inactive and to a certain extent have been confined to the nasal cavities, to the pharynx and elsewhere in a harmless condition suddenly to invade the meningeal spaces and there to produce such serious changes? In many cases this remains entirely obscure to us, in others preceding damages may be determined which in other infectious diseases we are also accustomed to look upon as *predisposing causes* of the affection.

If impartial clinical observation teaches that meningitis epidemics occur particularly in the cold season, the disbelief in the importance of *refrigeration* appears to me to be carried too far, if we attempt to deny the influence of the effects of cold upon the body. Occasionally meningeal phenomena so rapidly follow a previous refrigeration that any impartial person must recognize the connection between both occurrences; *injuries* also show a favorable influence toward infection. This need by no means always apply to head injuries; a marked shock to the entire body may result in epidemic cerebrospinal meningitis. It is worthy of note that occasionally quite insignificant injuries and shocks are sufficient to become dangerous to the affected person. For example, v. Leyden⁶ treated a young man suffering from epidemic cerebrospinal menin-

¹ H. Jaeger, Epidemiologisches und Bakteriologisches über Cerebrospinalmeningitis. Deutsche med. Wochenschr., 1899, Nr. 29.

² Huber, Demonstrationen mikroskopischer Präparate von Meningococcus intracellularis im Spinalleiter und Nasensecret eines Falles von epidemischer Genickstarre. Deutsche med. Wochenschr., 1897, Nr. 12, Bd. xxx.

³ E. E. Faber, loc. cit.

⁴ Thiercelind et Rosenthal, Sur un cas de méningite cérébrale à méningocoques avec septicémie. Société méd. des hôp., Séance du 27 Févr., 1899.

⁵ Councilman, Cerebrospinal meningitis. Boston Med. Journ., 1898, No. 7.

⁶ E. Leyden, Klinik der Rückenmarkskrankheiten. Berlin, 1874, i.

gitis in whom the first phenomena of the disease appeared shortly after the affected individual had dived during bathing. Twice I saw strong young men attacked by epidemic meningitis, in whom *mental over-exertion* had taken place; for a few weeks the one had been studying to pass his examination for admission to the University, and the other to be promoted into a higher class, both having studied until the early morning hours.

The meningococci can with great ease be prepared for identification under the microscope. The method by which I have prepared them is as follows: I spread some of the purulent exudate from the meninges upon a cover-glass, allowed the pus to dry in the air and then, holding the glass between thumb and forefinger with the pus surface upward, I rapidly passed it through the flame of a Bunsen burner several times. Then the glass with the pus-surface was placed downward and allowed to swim in a Löffler methyl-blue solution for fifteen minutes, washed in water and then dried in the manner previously described, in the gas flame of a Bunsen burner, and, finally, allowed to fall upon a drop of xylol—Canada balsam—which was previously placed upon a clean glass slide.

The preparation may be easily visible in an oil emulsion and with Abbe's condenser in 1,000 multiplication. The picture becomes especially clear and beautiful if a Zeiss apochromatic lens is used. Often in such a field diplococci will be seen, their dark blue bodies being surrounded by a clear ring, which has been looked upon as a capsule, so that the meningococci are often considered to be similar to pneumococci and they have been counted among the capsule-cocci, a circumstance that makes us understand that for some time both varieties of cocci were looked upon as the same structures. It must be remarked that, whereas the shape of the pneumococci may be quite properly compared with the flame of a candle, this comparison is not at all suitable for meningococci. Meningococci resemble half-globes which lie upon each other upon their diameters or have the shape of buns, they, therefore, remind us much more of gonococci, from which they, however, differ by other properties as we shall soon learn. In staining meningococci Huber advises staining dry preparations of the meningeal pus in carbofuchsin and then decolorizing them in water containing acetic acid. This is said to plainly stain the capsule of the meningococci. I possess no personal experience with this method of staining as I have had no recent opportunity of treating cases of cerebrospinal meningitis. Jaeger assumes, in his latest book that has been mentioned several times, that the capsule is an artifact due to the retraction of the body of the bacterium from its periphery, or to a mucoid excretion.

The typical picture of the meningococcus represents cells which contain small masses of meningococci, these cells very closely resemble those in which gonococci are present, which are often found in gonorrheal pus, but meningococci by no means spare the nucleus of the cell but enter it and destroy it, which never occurs in the case of gonococci. If meningococci are present in large numbers in the exudate they are also found collected in heaps, so that under these circumstances they may be easily confounded with staphylococci, not rarely are they collected in groups of four, or tetrahedral form, but they scarcely occur in the form of chains.

In contrast to pneumococci which stain according to Gram, they allow their staining material to disappear although slowly.

The production of pure cultures of meningococci from a purulent exudate or an inflamed tissue requires some care and practice, although meningococci flourish upon various culture media at the temperature of the body. Although they grow well upon Löffler's blood serum, upon agars streaked with human blood and upon glycerin agar, they have been seen growing upon ordinary agar, upon meat-peptone gelatin, which they do not liquefy, upon potatoes, upon human serum and in bouillon. Upon Löffler's blood serum there is noted after twenty-four hours, round colonies, 1 to 1.5 mm. in size, which are sharply demarcated, showing a whitish, mucoid and transparent appearance; upon agar plate cultures Weichselbaum found the superficial colonies thicker than the deeper ones; the latter were just visible to the unaided eye. The former under the microscope, in 80 times enlargement, showed a brown margin with a yellowish floor, which, toward the periphery, became pale up to the point of being almost completely colorless. The finer, deeper colonies appear round, possess a notched margin, and are of a brownish color. Upon gelatin plates only a sparse and very slow growth is noted. The colonies form fine points of a yellowish color, which upon microscopic investigation appear markedly granular, turbid and yellowish to yellowish-brown. In bouillon, even after twenty-four hours, turbidity occurs. After two to three days the bouillon again becomes clear, whereas a precipitate forms. In this, meningococci differ very markedly from staphylococci, which upon culture in bouillon produce a permanent turbidity. Crest formation resembling the comb of a rooster never occurs from meningococci. If pure cultures are spread upon potatoes the formation resembles that occurring in typhoid bacilli, the surface of the potato remaining unaltered.

An observation of the process of multiplication shows that the meningococci divide in two vertical directions so that they are arranged beneath and beside each other in rows or also in tetrahedral form; the latter arrangement is not rarely noted in meningeal pus.

In pure culture as well as in a dried condition meningococci retain their power of life for a very long time. Jaeger, for example, found that meningeal pus dried upon cotton and retained in Petri dishes for 127 days contained meningococci which were still capable of development. Under such circumstances it is even quite remarkable that epidemic cerebrospinal meningitis is not more frequently observed, and we are forced to the opinion that the human body does not show an altogether favorable culture medium for meningococci or, as this is more frequently expressed, the predisposition to the affection is not a great one. And still very frequently a slight touch is sufficient to produce contagion. That in the distribution of epidemic cerebrospinal meningitis *personal intercourse* plays a great rôle, was very easily confirmed, for especially in garrisons epidemics have been known to arise several times if a patient affected by meningitis entered the place. Contagion from other patients, nurses in hospitals, as has been described by Leichtenstern,¹

¹ *Leichtenstern*, Die epidemische Genickstarre (Meningitis cerebrospinalis epidemica) in den Provinzen Rheinland und Westfalen, mit besonderer Berücksichtigung der Epidemie in Köln im Jahre 1885. Centralbl. f. allg. Gesundheitspflege, 1893, Heft vi-ix.

for example, is less demonstrative as it concerned persons in a district in which the disease was present. Very reliable observations regarding the transmission of the disease have been reported by Petersen,¹ from an epidemic in Berlin, in which it was shown that not only intercourse with the sick but entrance into infected rooms was capable of transmitting contagion, and that contagion occurs even by means of a third person. According to the experiences of Panienski,² contagion also occurs by fomites, at least Panienski believes that an epidemic of meningitis was brought from Karlsruhe to Rastatt by material that was not disinfected.

It is not my object to present a complete and finished picture of epidemic cerebrospinal meningitis. The task that I have undertaken consists in emphasizing those modes of clinical examination which are the result of the latest methods of investigations. As carefully as I have described the bacteriology, so rapidly will I pass over the anatomical and clinical phenomena since they are readily found in any good work on the practice of medicine.

PATHOLOGY

In the membranes of the brain and spinal cord meningococci produce *anatomical changes* which are quite obvious, so that it is scarcely possible to overlook or mistake the affection. After lifting the bony capsule of the skull the dura mater is noted to be very tense, its inner surface appears dry and the sinus completely filled with blood, the free-lying convex surface of the brain gives the impression of being flattened as if a force acting from within had pushed it toward the internal surface of the skull; this is noted by a flattening and a broadening of the cerebral convolutions and a narrowing of the sulci.

The veins of the pia are choked with dark blood and are tortuous, and the finer branches contain so much blood that the entire surface of the brain attains a markedly reddened appearance, resembling an artificially injected specimen.

As especially distinguishing phenomena the permanent infiltration of the pia mater is added, very often yellowish, purulent streaks which accompany the filled pia vessels upon both sides, and here and there to a breadth of several millimetres, are noted. In further-advanced cases the pia mater shows extended opacity and briny and inflammatory edematous swelling and thickening. The acme of the changes consists in the entire superficial surface of the brain being covered by an extended coat of pus which is due to the fact that the tissues of the pia are profusely infiltrated with pus.

If the brain is taken out it will be noted that in the lower posterior cavities of the skull a profuse amount of *cerebrospinal fluid* has collected, which is turbid, shows the formation of flocculi, and not infrequently is of a purulent consistency, thereby proving inflammatory processes.

The *basal cerebral sinuses* contain much blood, which as a rule, is markedly coagulated.

¹ G. Petersen, Zur Epidemiologie der epidemischen Genickstarre. Deutsche med. Wochenschr., 1896.

² Panienski, Die Epidemie der Genickstarre in der Garnison Karlsruhe während des Winters, 1892–1893. Militärärztl. Zeitschr., 1895, Heft viii u. ix.

Upon the base of the brain the phenomena of purulent inflammation of the membranes is noted to a slighter extent than upon the convexity of the brain; the infiltration of pus appears to be more markedly developed in the areas situated between the pons, the cerebral peduncles and the optic chiasm.

Upon section of the brain the *cerebral ventricles* are often markedly dilated, obviously because they are filled with an unusual, profuse amount of cerebrospinal fluid. This cerebrospinal fluid is the cause of the pressure of the brain toward the internal surface of the skull, thereby giving rise to the flattening of the cerebral surface which was previously alluded to. The fluid of the ventricles also shows a turbid, flocculent, occasionally almost purulent, appearance and even the choroid plexus occasionally shows purulent infiltration. The wall of the ventricles of the brain is soft, of a friable consistency, showing so-called white cerebral softening.

The anatomical changes of the *spinal cord* are found to correspond to those in the brain. The dura mater spinalis especially in its lower portions is spread out and tense, upon palpation representing a soft bag. Upon section of the lumbar region large amounts of spinal fluid often squirt out in a stream, being of a turbid, flocculent and even purulent consistency, the pia is often turbid, showing purulent infiltration to a wide extent. With this the venous blood vessels are markedly filled and very tortuous; almost always the changes upon the posterior surface of the cord are more decidedly developed than those upon the anterior surface, which is probably entirely in consequence of the patient being constantly upon his back. It is worthy of note that the cervical portion of the cord-substance shows the slightest alterations.

The changes in the *substance of the brain and spinal cord* are often limited to a marked hyperemia, which in the brain is especially conspicuous upon the cortex. In other cases hemorrhages have developed, they are usually slight, most often only punctiform, but occasionally they are so close together that they must be designated as a focal affection, having a more or less great circumference. Occasionally areas of softening and even small pus foci are met with in the brain substance.

Upon a *microscopic examination*, the inflamed pia is noted to be markedly swollen, thickened, infiltrated with round cells, its blood vessels are dilated, completely filled with blood, and thickened vascular walls may be recognized that are infiltrated for the most part with round cells. Often vessels are found that are surrounded by tense round cell-heaps resembling cuffs around the hand, here and there dilated lymph vessels and lymph spaces are noted in the pia.

Purulent infiltration of the pia, as a rule, is sharply demarcated from the upper surface of the brain and cord substance but it is by no means seldom that it continues with those processes to a slight extent toward the internal parts of the brain and spinal cord, which originate from the pia. That independently of these septic areas in the pia the pus formation from the posterior parts of the cerebral membrane continues to the adjacent cerebrospinal substance upon the whole is rare.

Upon microscopic examination of the pathological tissues, meningococci should be looked for if, as occurs occasionally during life, it has not been possible to find these structures in the liquid obtained by lumbar puncture,

perhaps not even in streaked preparations which are made at autopsy from the meningeal pus. Naturally, the tissues to be examined must be first hardened in alcohol, then fine sections are to be stained with anilin colors in the usual manner.

Upon microscopical examination it may be readily recognized that the purulent infiltration has continued in a very marked and extended manner to the *spinal cord roots*. Such a continuation of the inflammation also occurs in the case of the *cerebral nerves*. The ear specialists quite properly emphasize that with extraordinary frequency, we might be almost tempted to say, quite invariably, suppuration from the acoustic nerve distributes itself to the internal ear and corresponding tracts have been noted of the optic nerve, the purulent condition being distributed to the eye.

As in most infectious diseases, so also in epidemic cerebrospinal meningitis, there is *granular opacity and fatty degeneration* even waxy degeneration, in the voluntary muscles, in the heart muscle, and in the cells of the glands, for example, in the epithelial cells of the urinary tubules, in the cells of the liver, in the cells of the mucous membranes of the stomach and intestines, as well as in the pancreas. On the other hand, quite in contrast to many other acute infectious diseases, *enlargement of the spleen* is by no means frequent, and it certainly does not belong to the regular anatomical findings. Berdach¹ who has observed an epidemic of meningitis in Trifail, Austria, calls attention to epithelial necrosis of the kidneys, which he quite properly refers to toxic causes.

Regarding the time which elapses between contagion and the appearance of the first symptoms of the disease, therefore, the *period of incubation*, but very few accurate observations are known. Evidently this period upon the average is from three to four days.

SYMPTOMS

The disease often begins without prodromes, manifesting itself by *repeated chills*, rarely with a single marked chill. In recent times attention has been called to the fact, that not rarely coryza, conjunctivitis, or pharyngeal catarrh have preceded as prodromes, and it is presumed that from these inflamed mucous membranes meningococci invade the cerebral membranes.

After a preceding chill, *fever* occurs, which usually reaches 102.5° F. and higher, at first showing a continuous type. Simultaneously disturbances occur which call attention to a severe implication of the brain. The patients complain of *vertigo* so that they can scarcely stand upon their legs, and, above all, a very intense *headache* is noted, which is often referred by the patient to the posterior part of the head, sometimes to the temple-region, sometimes to the top of the head, but which also in some cases is distributed to the entire skull. Occasionally this pain becomes exacerbated to such an extent that it is quite unbearable, which may be noted from the fact that from time to time the patient moans, sighs, or screams, holding the head between the hands; even when the patient is *unconscious* this moaning may be noted, and

¹ J. Berdach, Bericht über die Meningitisepidemie in Trifail im Jahre 1898. Deutsches Arch. f. klin. Med., 1900, Bd. lxxv.

he sometimes clutches at his head. Consciousness becomes more and more involved, and the patient either lies apathetic with closed eyes or is more or less wildly delirious. A phenomenon of the disease which is very valuable in the diagnosis is the *rigidity of the back of the neck*, this being often noted in examining the patients, in that the head, viz., the occiput, appears to be strongly pressed into the pillow. If the physician attempts to force his hand beneath the occiput and to bend the head forward, so marked a resistance is noted that the entire trunk is raised with the skull as soon as the latter has reached the horizontal axis of the body, often even sooner. This movement causes great suffering to the patient and even though comatose, he moans and his face becomes distorted from pain. Rotary movements of the head or more marked movements of the head posteriorly, on the other hand, may be carried out easily and without hindrance, producing slight pain if any at all.

The origin of rigidity of the back of the neck is most probably in connection with tonic spasm of the muscles of the nape of the neck, which in itself originates in an irritation of the anterior cervical nerve roots from the spinal meningitis. If the muscles of the neck are palpated they are found to be hard and contracted, and it can very readily be demonstrated that the trapezius is also implicated in this tonic muscular spasm.

For the same reason, as a rule, the extensors of the back are permanently contracted, which is shown by a stiffness of the vertebral column, and with an obvious curve of an anterior convexity, *opisthotonos*.

If toward the fatal termination the coma becomes intense, stiffness of the muscles of the neck and back not only relaxes but almost completely disappears, and this is to be looked upon as an unfavorable prognostic sign.

Pressure and even slight tapping upon the skull and vertebral column mostly produce decided pain which is even noted by comatose patients.

In fact *general hyperesthesia* is present; the patients are very susceptible to bright light and noises. Slight pressure upon the skin, muscles and peripheral nerve trunks is followed by a contraction of the entire body and an expression of pain.

The *face* of the patient, as a rule, is generally reddened. Especially does the *conjunctiva* appear to be injected with blood, occasionally there is even edema of the conjunctiva, *chemosis* develops, probably most often an inflammatory edema. In one of my patients I observed only left-sided chemosis, without there being local causes present at the autopsy to explain this phenomenon in the left eye.

Herpes labialis is extraordinarily frequent, appearing, as a rule, between the third and sixth days of the disease. Meningococci have not as yet been found in the contents of the herpetic vessels. In some cases the lips are not attacked by herpes, the eruption appearing in other parts of the face, most frequently around the alæ of the nose, or upon the nasal septum, even upon the trunk and upon the extremities in some cases.

Lips and tongue are dry and fissured, and in patients that are not carefully nursed these may be covered with dried blood and sordes.

Occasionally tonic spasm is noted in the masseter muscles and, as the result of this difficulty in movement of the jaw, even well-developed *trismus*. Clonic spasms in the pterygoid muscles not rarely lead to *grinding of the teeth*.

Apparently these phenomena are the results of an irritation of the fifth nerve.

In the respiratory organs no alterations are determined, except an *increase in respiratory frequency*, although bronchitis belongs to the most frequent symptoms of the disease. Sudden arrest of the respiratory movements, the so-called Biot's breathing, or an increasing and decreasing depth of the respiratory movement, with periodical pauses in respiration, so-called Cheyne-Stokes respiration, is much rarer in cerebrospinal meningitis than in tubercular meningitis.

The *pulse* not uniformly, but still quite commonly, in comparison with the height of the temperature, is slow. Toward the fatal issue it becomes so rapid that it can no longer be counted, probably as a result of paralysis of the vagus.

Regarding the *blood*, Williams¹ reports that among 32 patients, in an epidemic of cerebrospinal meningitis in Boston, 12 times he found a decrease in the number of leukocytes; this does not agree with the observations of v. Strümpell and Williams, who reported leukocytosis.

The *abdomen* is usually retracted. As the abdominal coverings are not especially tense it is probably not due to a clonic spasm of the abdominal muscles but to a voluntary spasm of the muscles of the intestine; from the spasm of the intestinal musculature the obstinate *constipation* can be explained from which some patients suffer.

In some patients frequent *vomiting* is noted.

The conditions of the *urine* are conspicuous in that in some cases, in spite of the existing fever, the urine is voided in large amounts, being of a light yellow appearance. It frequently contains albumin, and in some few cases glycosuria has been observed.

The behavior of the *patella tendon reflexes* varies and is of no importance, absence of the patella reflex is not infrequent, but this occurs usually only toward the fatal issue.

Upon stroking and palpating the skin, very frequently marked irritability of the *vaso-motors* may be noted. The skin reddens to a marked extent, this appearance being maintained for quite a long time after palpation or after slight stroking.

The symptoms of meningitis have been enriched in the last few years by the development of *Kernig's symptom*, namely, the fact that if the patient is propped up in bed, flexure movements of the legs and arms occur in the hip and knee joints, occasionally also in the arms. The diagnostic value of this sign must not be overrated, for Giuseppe² quite properly emphasizes that it is occasionally absent in cerebrospinal meningitis, whereas, on the other hand, he has seen it in tubercular meningitis and in sinus thrombosis. Occasionally this sign may even be noted in convalescence, remaining for some time. Roylet³

¹ Francis H. Williams, Seventy-one cases of cerebro-spinal meningitis. Med. and Surg. Rep. of the Boston Hosp., 1898, ix.

² M. Giuseppe, Il fenomeno di Kernig come mezzò diagnostico preziosa nella meningite cerebro-spinale. Gazz. Lombard., 1900, p. 171.

³ P. Roylet, Le signe de Kernig dans les méningites. Gaz. hebd. de méd. et de chirurg., 1900, 15 Juli, No. 56.

looks upon this symptom as nothing else than the result of irritation of the spinal cord and cord roots due to increase of the intraspinal pressure or immediately due to the purulent exudate.

COURSE AND VARIETIES

The *course of epidemic spinal meningitis* is usually acute. If the disease terminates fatally, death occurs most frequently at the end of the first week of the disease. Death usually results with the increase of coma and the other signs of increasing cerebral pressure, sometimes also from complications. In some cases, without especial complications appearing, the disease continues for an extraordinarily long time, so that an irregular and varying increase in temperature continues for six and even nine months.

In contrast to this, cases occur that run their course in a few hours, which are designated as *meningitis cerebrospinalis acutissima s. siderans*. Cases have been observed in which farmers who were perfectly well in the morning, going out to their work have been suddenly attacked by vertigo and headache, rapidly becoming comatose and dying in a few hours. At the necropsy of such cases a marked hyperemia of the cerebral vessels is noted; as the duration of the disease was too brief, suppuration did not occur.

As an *intermitting form of cerebrospinal meningitis*, such cases have been described in which fever and nervous disturbances alternate with a certain degree of regularity, which remind us somewhat of the course of a malarial intermittent. The older physicians were not averse to regarding this as a combination with malaria but there can be no question of this. Since we have learned to recognize the malaria plasmodium as the exciting cause of malarial fever, we have reached the unalterable conviction that in an intermittent meningitis, these organisms do not come into question.

It is very important to know that in time of a meningitis epidemic, numerous *abortive and mild types* occur which are characterized only by slight vertigo, headache, corporeal and mental lassitude, and by psychical depression, associated with great sensitiveness to impressions affecting sight and hearing. This will scarcely be observed at other times, but during the prevalence of a meningitis epidemic they require very careful consideration, for if these cases are not carefully observed and treated the clinical picture may take a very serious turn and death result. Besides such patients are dangerous to their surroundings, as they distribute contagion which may be followed by a very severe attack of the disease.

Cases which arise resembling cerebral hemorrhage, causing sudden loss of consciousness and paralysis, have been designated *meningitis cerebrospinalis apoplectiformis*.

COMPLICATIONS AND SEQUELS

Various *complications* occur in epidemic cerebrospinal meningitis and, as in other infectious diseases, some epidemics show many, other epidemics but few. If we desire to gain a clear picture regarding these complications, we must remember that some of them are connected with disease of the nervous

system, whereas others depend upon propagated or metastatic inflammation, the last giving rise to severe general infection.

Among the *complications on the part of the nervous system* are irritative and paralytic manifestations of the various cranial nerves and nerves of the extremities. Frequently the former are first noted, being followed by the latter. Occasionally *nystagmus* is seen, to which, in the further course of the disease, *paralysis of the muscles of the eye* is added. Contraction of the *pupils* is later followed by dilatation; frequently there is inequality of the pupils. Occasionally *facial spasm* is noted and later paralysis of the muscles of the face appears. *Clonic contractions and paralysis of individual extremities*, occasionally unilateral paralysis, are observed. The paralyzes often vary greatly regarding the severity, so that we have the impression that they are due to various pressure conditions by meningeal exudates, perhaps they also owe their origin to variations in circulatory conditions. At the autopsy a clear insight as to what has caused these paralyzes is by no means always obtained. In children at the onset of the disease *general clonic muscular spasms with unconsciousness* is observed.

Complications as the result of the propagation of the inflammation are sometimes noted in the eye. Among these may be counted *optic neuritis and neuro-retinitis*, which is observed in about one-fourth of the cases. Marked filling and swelling of the retinal veins point, besides, to a difficulty in circulation which has been produced by the meningeal exudate in the course of the sinus cavernosus. Occasionally dangerous conditions of purulent *iridocyclitis* form which lead to permanent blindness and disappearance of the eye. Oeller and Axenfeld¹ are of the opinion that these inflammations of the eye are not due to a propagation of the process but are of metastatic origin.

The *ear* is affected with extraordinary frequency. *Purulent otitis media*, with rupture of the pus through the tympanic membrane, is not an unknown phenomenon. But even without such a rupture the internal ear may be severely diseased and complete loss of hearing develop. If this unfortunate result occurs in both ears in children that have not yet learned to talk, *bilateral deafness leads to mutism* as a sequel.

Among the *metastatic inflammations* which occasionally arise as complications of an epidemic cerebrospinal meningitis, we must differentiate between those that are due to the meningococcus and those which are due to a secondary infection from other inflammatory agents, most frequently probably with the streptococcus pyogenes. Whether the one or the other condition is present can only be determined with certainty by a bacteriological examination of the products of inflammation. That the contents of *inflamed joints and pneumonic exudates* contain meningococci has been previously emphasized.

As the result of *severe general infection*, marked cardiac asthenia develops, occasionally phenomena of the general *dissolution of the blood* are noted, which may be discerned from hemorrhages into the skin and the various mucous membranes.

¹ Th. Axenfeld, Ein Beitrag zur Entstehung der Augencomplicationen, besonders der eiterigen Entzündung des Bulbus bei der Meningitis cerebrospinalis suppurativa. Monatschr. f. Psych. u. Neurol., 1897.

Among the *sequelæ of epidemic cerebrospinal meningitis* there must be primarily mentioned long-continuing and even permanent *nervous disturbances*. Vertigo, headache, lassitude, after mental effort, loss of memory and similar conditions are complained of by most patients for many months and even years after the disease. Weakness and paralysis of individual nerves or of the extremities must be counted as among the sequelæ; the severe permanent disturbances of the organs of special sense (sight, hearing) have been previously mentioned.

The development of *chronic hydrocephalus* which I have seen occur in some patients who have recovered from an attack of purulent meningitis deserves special note; this complication gives rise to very serious results. These consequences vary according to whether the condition develops in a child in the first years of life, when the skull does not as yet contain ossified sutures and is, therefore, capable of distention, or in an adult with an unyielding skull.

In an infant scarcely a year old I noticed the gradual development of a hydrocephalic skull, the like of which I had never seen before. The unfortunate patient, finally, could no longer hold his balloon-like dilated head erect upon his vertebral column and became mentally weaker and weaker. In this unfortunate condition I observed the child for nearly a year, I then changed my residence and have never learned what finally became of him.

I observed three adults that had recovered from all phenomena of a severe cerebrospinal meningitis. After they were free from fever for weeks and believed themselves completely restored to health, they were allowed to leave their beds and walk around in the corridor; in all of them the further course developed in a similar manner, for example, the patient arose in the morning apparently well and in the course of the forenoon went into the garden, suddenly he complained of an unbearable headache and after a few minutes lost consciousness; the temperature rose to 102.5° F., and he died within eight to twelve hours. At the autopsy the only anatomical change noted was a marked internal hydrocephalus, with dilatation of the cerebral ventricles, and a flattening of the surface of the brain.

DIAGNOSIS

For the physician who looks upon the meningococcus as the sole generator of epidemic cerebrospinal meningitis, diagnostic endeavors have to-day been decidedly changed and amplified. To the former purely *clinical diagnosis* the *bacteriological diagnosis* has been added as a determining factor.

From a purely clinical standpoint the diagnosis of a purulent cerebrospinal meningitis is not difficult. In contrast to tubercular meningitis, purulent cerebrospinal inflammation is characterized by the fact that the latter begins suddenly, runs its course with high fever, shows a more *fulminant course*, frequently attacking robust and healthy persons, whereas the patient suffering from tubercular meningitis frequently shows tubercular changes in other organs. If in the course of a meningitis, *herpes facialis* occurs, tubercular meningitis cannot be excluded with absolute certainty but it is extremely unlikely. On the other hand, the appearance of *choroid tubercles* is absolutely in favor of tubercular meningitis.

Whether a substantive, i. e., a purulent meningitis not due to pre-existing disease is a meningococcus meningitis or owes its origin to other inflammatory agents, can only be determined with certainty during life by a *bacteriological investigation*. The appearance of meningitides in plentiful amounts is not yet absolutely certain proof of a meningococcus meningitis, and has also been observed in pneumococcus meningitis, although in the latter instance the epidemic scarcely shows such an extended distribution as is frequently the case in epidemic cerebrospinal meningitis. Especially in individual cases the bacteriological investigation is absolutely necessary for diagnostic purposes. If, as occurs frequently, meningococci are found in the nasal secretions, in the mucus from the pharynx or bronchi, or in pus from the ear, in the case of meningococcus meningitis we must still remember that they occasionally occur in other patients so that the determination of meningococci does not yet decide the diagnosis with certainty.

The conditions are different if we decide upon *lumbar puncture* and the cerebrospinal fluid obtained in this way is examined for meningococci. We must, therefore, declare lumbar puncture to be an indispensable aid for a positive diagnosis. Presupposing care and practice, it is almost a harmless maneuver. Naturally, the first requirement in lumbar puncture is that cerebrospinal fluid be obtained, which, in spite of carrying out the procedure accurately, is not always accomplished, as occasionally the fluid is not under the influence of increased pressure or no fluid is present at all in the subarachnoid space of the spinal cord. Whereas in the case of tubercular meningitis the fluid obtained is usually as clear as water and only after several hours standing shows a veil-like coagulum, in the case of purulent meningitis the fluid is turbid, flocculent and may even be conspicuously purulent. The pus which has formed under the influence of meningococci is frequently noted in the bacteriological investigation of the *smear preparations upon cover-glasses*, and I should like to advise centrifugating the punctured fluid and examining the sediment bacteriologically. The finding of meningococci would be decisive, but we must be prepared for mixed infection with pneumococci, streptococci, staphylococci and influenza bacilli. It is self-evident that we dare never limit ourselves to the investigation of a single cover-glass preparation if meningococci are not found upon the first specimen, but at least a dozen preparations must be carefully examined before further microscopic endeavors are abandoned.

If, in spite of this, we have not attained success, endeavor must be made to obtain *pure culture* and those difficulties must be obviated which arise from the easier and more luxuriant growth of pneumococci and staphylococci. As a favorable culture medium for meningococci, besides Löffler's blood serum, especially agar coated with human blood may be employed.

Occasionally, pure cultures are also negative, in spite of the existence of a meningococci meningitis, then nothing remains but in the case of a fatal termination to examine the exudate and the tissues again microscopically and by culture, and in this investigation the fluid of the cerebral ventricles is to be especially examined.

To properly present the difficulties of diagnosis, it should be remembered that occasionally in tubercle meningitis a *mixed infection with meningococci*

occurs, so that it is quite likely that, besides tubercle bacilli, also meningococci may be found in the lumbar fluid.

A confusion between epidemic and *serous cerebrospinal meningitis* will only rarely occur, as in the latter case the lumbar puncture fluid remains completely transparent.

PROGNOSIS

Epidemic cerebrospinal meningitis (meningococci meningitis) under all circumstances is a very serious disease and every cautious physician will, therefore, give a guarded prognosis. As in other infectious diseases, so also in cerebrospinal fever, different epidemics show a very varying death rate, but still the mortality is usually from 20 per cent. to 85 per cent. In spite of this, however, epidemic meningococcus meningitis, after all that we know in comparison to pneumococcus meningitis, is a comparatively favorable affection for pneumococcus meningitis almost invariably terminates in death.

In general the prognosis will be the more unfavorable, the more marked the phenomena of intracranial pressure, especially deep coma, galloping pulse and paralysis. Severe general infection also renders the prognosis unfavorable. Wentworth¹ emphasizes that there is no connection between the lumbar bacteria and the amount of pus present in the meninges, that, however, the disease is the more serious the greater the amount of pus. Even in such patients as have escaped all the dangers of the acute affection, the prognosis is sometimes unfavorable as chronic hydrocephalus may lead to death or in other cases severe incurable sequelæ may remain as consequences.

Bacteriological investigations regarding the causes of disease are not only of theoretical but also of practical value. Only the investigations of Robert Koch regarding the comma bacillus—named after him—that was found to be the pathogenic agent of Asiatic cholera, and after the biological properties of this organism had been ascertained, made it possible to prevent the entrance of cholera from Hamburg into Germany a few years ago, and we owe Koch permanent gratitude that he himself proposed and enforced the preventive measures which at that time made it impossible for the cholera bacillus to gain a foothold in Germany. In regard to cholera alone, how many thousands and thousands without question owe their lives to the bacteriological investigations of Koch. The conditions are quite similar in tuberculosis, in which the conflict, although only commenced a short time previously, is even to-day not without significant results, and probably in the near future will lead us to still greater victories. A disease in which we know the causative agent, we may combat with courage and with greater hope of success. Quite properly there should be statistics made upon bacteriological examinations, in particular as regards preventive measures (prophylaxis).

PROPHYLAXIS

If a proper prophylaxis is intended to be carried out in the case of cerebrospinal meningitis, it is necessary as in many other infectious diseases to make the attempt to recognize the first and isolated cases quickly and with cer-

¹ A. H. Wentworth, Epidemic cerebro-spinal meningitis. Lancet, October 1, 1898.

tainty, as from these, in case they remain unobserved, often widespread epidemics take their onset. This is only possible, as we now know, by bacteriological investigation. Naturally, no practical advantage accrues from the diagnosis alone of an epidemic cerebrospinal meningitis, for further effort must be in the direction of making the patient innocuous to his surroundings and of eliminating all danger of contagion. External circumstances mostly prevent us from carrying out this indication properly. It would naturally be most expedient to permit the patient to remain in his home, which is already infected, and, if possible, to send all the other inmates to another house or, even better, to a different but healthful locality, where they may remain under observation, their dwelling to be isolated and carefully guarded. So also the room and house of the diseased person must be quarantined and strangers prevented from entering.

As a rule, quite the opposite process is observed; the patient is brought to a hospital and his belongings are allowed to remain in the house. All rooms in the house in which the patient has been should be carefully disinfected, which may be easily accomplished by the use of sterilizing apparatus; clothing, linen, and all objects that have been used by the patient are also to be sterilized, steam apparatus being most suitable for this purpose.

If a patient with epidemic cerebrospinal meningitis remains in his own dwelling this should be quarantined with all of its inmates, as a transmission of meningococci may occur through a third person. Later on, the disinfection of the room and its contents must be carried out; the residents of the dwelling should first take baths and put on disinfected clothes before they are allowed to communicate in the usual manner with other persons.

Under no circumstances is it allowable for children from houses in which cases of cerebrospinal meningitis occur to attend school or mingle upon playgrounds with other children, as they may transmit the disease even while remaining healthy themselves.

Physicians must make it their duty to visit their meningitis patients last and then to carefully disinfect themselves.

In hospitals meningitis patients must be isolated for, as has been previously emphasized, contagion may occur in other patients and in nurses. Secretions from the nose, and the bronchial tubes, the urine and a possible discharge from the ears must be disinfected. The caution of disinfecting the stools with milk of calcium is necessary, as Jaeger has observed meningococci in the enlarged lymph follicles of the intestinal mucous membrane.

Visits to patients are to be prohibited under all circumstances.

If epidemic cerebrospinal meningitis is present in a certain district, measures should be taken to prevent gatherings of people in assemblies of any kind.

Regarding the *individual prophylaxis* at the time of an epidemic of meningitis, bodily and mental emotion, injuries of all kinds, especially head injuries, are to be carefully avoided. Abuse of alcohol is to be absolutely prohibited. It is advisable after the principal meal to cleanse the oral cavity by means of a mild disinfectant solution and also to spray the nose morning and evening. Whether it will be possible to produce an immunizing serum and by its injection to prevent contagion will be shown in the future.

TREATMENT

Most important is the *nursing of the sick*. A quiet and slightly darkened room is absolutely necessary, *nourishment* should be fluid and non-irritating; a milk diet is especially indicated. *Ice bags* are to be laid upon the head and along the vertebral column, for this diminishes the headache and is said to control the inflammation; other *antiphlogistic agents and derivatives* (leeches, cantharides plaster, mercury salves, painting with tincture of iodin, calomel internally, and similar substances) are used, with exceeding rarity. The same is true of resorbing remedies (potassium iodid, salve containing potassium iodid or iodoform). On the other hand, anodynes are indicated and appear to be most valuable and I use them with a free hand. If the pains are not very marked great relief is frequently given by the administration of phenacetin, antipyrin, sodium salicylate, lactophenin ($7\frac{1}{2}$ to 15 grains three times daily), but a time almost always occurs in which it is necessary to employ subcutaneous injections of morphia which are to be given in sufficiently large doses to alleviate the pain and give the patient rest. If the pains recur morphia injections are to be repeated from time to time.

Lately propositions worthy of note have appeared regarding the treatment of meningitis; first, among these, *lumbar puncture* is to be mentioned, which, after being carried out, occasionally causes the disappearance of the coma and alleviates headache. A curative action cannot be expected from lumbar puncture.

Osler¹ reports a successful *surgical treatment* of epidemic cerebrospinal meningitis. Laminectomy was performed and pus was removed by a subdural irrigation by means of a physiological salt solution.

Aufrecht² saw favorable results from hot baths (temperature of 104° F. of ten minutes' duration); the same results were observed by Woroschilsky³ and Wolisch.⁴ I have used hot baths in two patients without success, but I must admit that the condition of the patients was the most serious that could be imagined.

Whether the experience of Vohryzek⁵ of administering pilocarpin hydrochlorate (0.07 to 200, a tablespoonful every hour) internally, will be found valuable, the future alone can tell.

[See also Serum Therapy, page 909.]

¹ William Osler, The arthritis of cerebro-spinal fever. Boston Med. Journ., 1898, No. 26.

² D. Aufrecht, Heisse Bäder bei protrahirtem Verlauf einer Meningitis cerebrospinalis. Therap. Monatshefte, 1894, p. 381.

³ Woroschilsky, Anwendung von heissen Bädern in zwei Fällen von Meningitis cerebrospinalis. Therap. Monatshefte, Februar, 1895.

⁴ Alfred Wolisch, Zur Behandlung der Meningitis cerebrospinalis mittels heisser Bäder. Therap. Monatshefte, Mai, 1896.

⁵ V. Vohryzek, Ueber einen mit Pilocarpin behandelten Fall von Meningitis cerebrospinalis epidemica. Allg. Wiener med. Ztg., 1895, Nr. 8.

DIPHTHERIA AND DIPHTHERITIC CROUP

BY A. BAGINSKY, BERLIN

DIPHTHERIA is a *contagious* disease, directly transmissible from child to child, also indirectly from a third person and infected fomites. It is one of the most terrible scourges, and has appeared in decimating epidemics which are scarcely equalled by any other affection in the history of medicine. It is not our purpose at this point to report them, and we must refer to special publications regarding this point. From these it can be seen that the first epidemics go far back into ancient times, that the disease bore the name "Morbus ægyptiacus," and "syriacus," that on account of its terrible character Spanish authors gave it the name "*Garotillo*" (so-called after the cudgel of the executioner)—and, on the other hand, by Swedish physicians it was given the name "*Strypsjuka*" (strangling disease). From these designations, which were popular with the people, it may be seen that the danger of suffocation was the most prominent symptom of those affected, and that death by suffocation was the most feared result. And yet so many other characteristics were found in the ancient descriptions of the disease: The rapid prostration, the decline in the cardiac power, the condition of delirium, etc., jactitations, effusions of blood, etc., which all point to the fact that still another element other than the purely mechanical hindrance in respiration was included in the disease, and showed itself prominently by causing death. And this was perhaps the reason that, according to the mode of its appearance in one or the other form, two different diseases were distinguished, and the actual suffocating disease which was later designated as "croup" by the Scotch, was differentiated on the other hand from that form which apparently caused death by *poisoning*. The clinical picture of the disease varied in spite of the plentiful opportunity for its observation, up to that time in which the great French physician, Pierre Bretonneau, combined the whole, and from a number of classical observations that could not be surpassed, called attention to the *unity of the various forms*, in that he showed the combination of the appearance of thick leather-like membranes in the mouth, pharynx and naso-pharyngeal space, and with the changes in these structures, malignant and deleterious symptoms at the same time were present. Bretonneau had attached the greatest importance to these membrane-like pathological formations, and also originated the name diphtheria (from *διφθέρα*, the skin, which the disease has retained).

After these brief remarks regarding the name of the disease, we shall at once consider the clinical course and observe the manifold pathologic pictures which are combined in this conception of a substantive disease which shows so many anomalies. Unfortunately, the number of cases in every large

hospital that treats this disease is so great and varying that it is possible to demonstrate almost everything which is designated as belonging to the diphtheritic process, even all the sequels and complications of the disease.

Case History.—Boy aged three years, showing some pallor, apparently well nourished, with a moderately high temperature (101.3° F. to 102.6° F.), admitted to the hospital yesterday. The history did not show accurately the time at which the boy was taken sick, but the onset of the disease could not have been long ago as the little patient appeared to be well a few days previous, ate and played. It can be heard from his crying that he has a clear voice, nevertheless, the tone is somewhat changed, it may be expressed as pharyngeal. Upon observing the throat externally, it appears to be somewhat thickened; upon palpation two glands at the angle of the jaw are enlarged almost to the size of walnuts; apparently they are painful. The skin of the patient shows a normal color, is not especially hot nor dry, nor is there marked perspiration. The physical examination of the thorax and abdomen shows nothing abnormal. The pulse is soft, but little tenseness in the radial artery. The pulse rate, upon which little importance must be placed in children, as it varies greatly under slight emotional conditions, is somewhat over 100 per minute.

Upon examination of the mouth and *pharynx* it will be noted that the lips are dry, slightly covered with sordes; the tongue is red at the margins, white upon its upper surface. Upon opening the mouth wider, there are noted upon both tonsils and posteriorly on the wall of the pharynx a *thick, grayish-white coating*, arising from the surrounding tissues, apparently tightly adhering to the surface. The mucous membrane which has remained free is of a pale red color, not too darkly tinged, therefore, not specially inflamed, still it is swollen, perhaps slightly transparent as if moistened through and through.

This corresponds with the classical description given by Bretonneau—"Diphtheria, a membranous coating which covers the pharynx."—The child has diphtheria.

Before answering the question, "How has this disease originated, and to what symptoms does diphtheria give rise?" let us attempt to form a picture of the course of this, apparently, by no means terrible affection.

This can be seen from a *second case history*. Child about three years old, has been under treatment for a few days; it showed the same symptoms as the former case when admitted, but at a glance it can be seen that it is of an entirely different, much less severe type. Yet, if we did not know that a few days ago it was seriously ill, we should scarcely take it for a sick child on account of its joyful, happy disposition. The temperature curve of the child shows that the temperature, which was originally somewhat over 102.2° F., has gradually fallen to between 98.2° F. and 99.5° F. The pulse is soft, still over 100 per minute. There is no impediment to the respiration; the voice, as may be noted when the child speaks, is pure and the physical examination of the respiratory organs shows nothing abnormal. The two submaxillary lymph glands at the angle of the jaw, that can scarcely now be felt, are but slightly conspicuous. The lips are smooth, of a pale red color. The tongue is still slightly coated. The pharyngeal mucous membrane appears upon the whole to be of a somewhat deeper red than normal. The tonsils are larger than normal and appear dark red, and upon close examination we still note here and there individual grayish-white streaks lying upon them, whereas the rest of the pharyngeal membrane appears red. Upon the posterior wall of the pharynx a broad thread of mucus of a yellowish-gray consistence is noted. This is all that remains of the original grayish-white, thick membrane. The examination of the urine shows that there is nothing abnormal, especially no albumin is present. This has all occurred *under the influence of an effective therapy*, the diseased process having given way to an almost normal condition, and we are entitled to hope that nothing will occur which will prevent the speedy return of the entire process to complete health.

Upon the basis of these two clinical histories, we shall enter upon a general discussion of the affection.

Diphtheria is a disease that is communicable; it usually begins with fever and commonly arises from the pharyngeal organs or often from the nasal mucous membrane. It is characterized by pseudo-membranous yellowish-gray or dirty gray deposits which are adherent and invade the mucous membranes, showing a tendency to distribute themselves. The disease may appear in the mildest form, although with some little fever, with but relatively slight implications of the general organism, and so appear and run its course as a *local disease of the pharyngeal structures*.

The disease is not limited to *climatic or geographical locations*, it has appeared in the coldest as well as in tropical and subtropical regions, and everywhere has shown an epidemic distribution. Nevertheless, we cannot suppress the impression that the affection shows a preference for the temperate and northerly zones; at least it shows itself there more frequently than in others, and its epidemics are of longer duration and perhaps also more severe. The highly situated portions of the different localities show no exemption from the appearance and distribution of the disease, neither does the constitution of the ground have an influence; the inhabitants of swampy areas are affected to the same extent as those of the mountainous regions, the inhabitants of sandy and gravel districts as well as those dwelling upon more compact earth.

The question has been much debated whether *season* favors the distribution of diphtheria. Unquestionably the months of the winter are those in which the affection appears most frequently and most severely, and in which it attains its greatest distribution; still there is frequently enough an opportunity of observing the severest epidemics in summer, and I can still recollect with horror the first epidemics that I saw in the summer among the population of the country. However, it is possible that the affections of autumn and winter, particularly the catarrhal implication of the pharyngeal mucous membrane, produces a predisposition to the disease.

The affection scarcely ever manifests a preference between rich and poor, and affects those living under the best hygienic conditions, even the members of royal families having succumbed to the malady. Naturally, the unfavorable mode of life of the poor, the bad housing, crowding together, and the uncleanness which goes hand in hand with these, favor the distribution of the disease. However, it cannot be proven with certainty what was formerly generally accepted, that bad ventilation of rooms alone, or faults in flow of dirty water and gases from privies, favor the distribution of the disease.

The affection occurs at any *age* and is widely distributed; the cases are by no means rare in which parents are simultaneously attacked with their children, and in which the disease is frequently communicated to physicians from their little patients. Regardless of all this, the disease specially seeks the youthful and is most dangerous in them. According to our own observations, children in the first year of life are but seldom affected, but as early as in the second year quite large numbers are attacked; a maximum morbidity and also mortality figure is shown by the period from the second to the fifth year of life. This corresponds also to the observations of other investigators.

They have not been able to determine that *sex* shows any difference in the predisposition to the disease, on the contrary, boys and girls are equally affected. Neither do different *constitutions* show a variation in predisposition; but one point must be observed, that especially such children as suffer from chronic catarrh of the nasopharyngeal space, from enlarged tonsils and adenoid vegetations are attacked; also certain *pre-existing affections* produce an increased *predisposition*, such as measles, and, above all chronic nervous diseases, such as poliomyelitic paralyses, hemiplegias, etc.

On the other hand, the very remarkable fact has been discovered that there are persons that are actually immune to the disease; and it is probable that this *immunity* is due to a peculiar constitution of the blood serum.

As has already been emphasized, the disease is *contagious from person to person*. The pathogenic organism, however, also adheres to fomites, such as clothes, toys, and may be transferred by means of them. But the transmission by this means occurs to a much slighter extent than by direct contact. Curiously, in spite of the daily experience regarding this contact-infection, there are some physicians who doubt this property, and just such instances have occurred in which physicians were infected, and these are more convincing than any others. Even Bretonneau mentions cases of this kind with a fatal outcome, and any physician of experience is able to relate some very dangerous examples of that period when it was not yet possible to take early and decisive measures against the disease. If in our practical activity, attention is paid to these points, we will note daily examples of transmission among children of the same family, school children, and from servants and nurses to children of the family. The most unpleasant and even momentous circumstance is this, that adults who do not appear to be seriously ill and only suffer from mild forms of angina may transmit the most severe forms of the disease to children. For example, some years ago my own child was infected by a servant who I ascertained afterward had visited her sister affected with diphtheria, the servant in question suffering from an angina which she had concealed from me. The cases are well known in which the further dissemination of the disease has been promoted by children affected with diphtheritic disease attending school. As slight as the transmission by fomites may be compared to the *transmission by direct contact*, this must, nevertheless, be admitted. We may assume as quite certain that transmission occurs by means of infected food products, milk, etc., although it may be difficult, in the individual case, to determine this mode of distribution of the disease.

How this transmission and dissémination occurs will be readily understood when we come to describe the cause of the disease, **the bacillus of diphtheria**. It is well known that after much fruitless and discouraging labor, after prolonged search, Löffler, in 1884, succeeded in cultivating a bacillus from the membranes of diphtheria, which had been previously noted by Klebs and described by him as the likely cause of the disease, but which still lacked an invariable demonstration, and for this reason was not fully proven. Löffler described the bacillus as a *constant finding* in the dense pseudo-membrane of typical cases of diphtheria; in small heaps below the surface of the pseudo-membranes where the bacilli are present in large numbers they take an intense stain with the Löffler color-mixture. Löffler also

gave the elective mode of cultivation upon a blood serum mixture, which since then has shown itself to be the best culture medium for the bacillus. The mixture consists of 3 parts of calf's or lamb's serum, 1 part of neutralized veal bouillon, 1 per cent. of peptone, 1 per cent. of grape sugar, and $\frac{1}{2}$ per cent. of table salt. The bacillus shows itself as a club-shaped organism $1\frac{1}{2}$ to 2.0 microns long and 0.3 to 0.5 microns thick, usually as double rods so situated that they are joined at an angle (compare the illustrations, Figs. 34 and 35). In pure culture the microbes present a special appearance; the latter is somewhat characteristic in that the rods for the most part are parallel to one another, showing a palisade arrangement.

I cannot enter here upon the other special peculiarities of the bacillus, nor upon the many and manifold doubts which were thrown upon it, especially after a bacillus was discovered that resembled it, which was finally designated as the *pseudo-diphtheria bacillus*, which is, however, non-virulent, whereas the utmost virulence is a peculiarity of the diphtheria bacillus, and was proven in the most certain and convincing manner by Löffler in animal experiments. The diphtheria bacillus grows luxuriantly upon the slanting Löffler serum, in a few hours becoming microscopically visible, showing a pale, yellowish-green, vapor-like streak which appears finely granular upon the surface, or in wavy forms, with small roundish furrows upon the borders.

What appeared to oppose Löffler's important findings was primarily the fact, that succeeding investigators did not always find the bacillus in all cases diagnosticated as diphtheria, until finally Roux and Yersin in Paris demonstrated its presence in methodical examination, first in 61 certain cases of diphtheria, whereas in 19 others which originally had the appearance of diphtheria, but in their further course showed themselves as non-diphtheritic, it was absent. Simultaneously with the French authors, we began our own investigations in this hospital and we succeeded in demonstrating that the Löffler bacillus was always present in cases which showed a severe course, whereas those cases that were looked upon as diphtheria, but in which the bacillus was not present, showed an entirely different, i. e., more favorable course, a fact which was proven by all our further investigations. Hence we could say with absolute certainty that the Löffler bacillus, in the cases admitted to this hospital in which a diagnosis of diphtheria had been made according to the clinical findings, was absent in scarcely 3 per cent., and in those cases in which upon repeated careful examinations the Löffler bacillus was not found, with but very isolated exceptions the clinical course showed that they were *not cases* of diphtheria. This assured the significance of the bacillus as the pathogenic agent of diphtheria and not the slightest contradiction to this fact can be advanced, even to the present time, for the bacillus is found upon mucous membranes upon which no pseudo-membranes are present, and in which no actual symptoms of disease can be demonstrated. This latter fact, on the contrary, is connected with the immunity of the culture media in individual human beings, and no less so with the greatly varying virulence of the bacillus, which like all pathogenic bacteria without exception is very unstable and varies greatly; this, however, does not in any way alter the clinical facts that have been determined and they must be adhered to.

I may assume that it is well known that the bacillus shows certain properties which explain the manner of the distribution of the disease such as its extraordinary tenacity of life, how it flourishes in milk, how it adheres to fomites, such as under-clothing, boots, clothing, etc., further its property of growth in association with streptococci, bacillus coli, bacillus proteus, etc., in which it has even been shown that some of the previously mentioned organisms are occasionally capable of increasing the symbiotic growth of the virulence of Löffler's bacillus, or to rekindle it. On the one hand, this explains the transmission of the disease by fomites, of which we have already spoken; on the other hand, the upflaring of severe epidemics at one point and the milder course of the disease at another point. Let us consider for a moment the mode of action of the bacillus in the affected organism. Obviously, the pathogenic agent changes into a morbid condition the affected mucous membrane at the point of its attack, which process may be recognized in the appearance of the diphtheritic pseudo-membrane. What is this pseudo-membrane anatomically, and how does it arise?

The anatomical changes in the mucous membranes which are attacked by the pathogenic agent and the pseudo-membranous formations have been for a long time the objects of closest observation, without complete unanimity of opinion having been attained even to-day. We cannot repeat in detail the various differing opinions, and I may refer, as I believe, to my rather exhaustive compilation in my book upon diphtheria and croup.¹ I can only repeat here that it is due to a high grade of degeneration of the vessels and fibrinoid degeneration of the connective tissue, causing a fibrinous exudation, the products of which, upon the surface, are subject to necrosis and absorption, becoming a granular mass; with all this there is a dissemination of the entire new-formed mass, of the bacillus and other more accidental microbes (streptococci, staphylococci, bacillus coli, etc.). Therefore, in a combination of necrosis with exudative fibrinous desquamation, what is especially conspicuous is the extraordinarily great tendency to the propagation of the process, so that the membranes, as already described by Bretonneau, appear to "flow downward," although they are tightly adherent and the mucous membrane is altered to some distance below the surface.

The distribution of the process to the larynx, trachea and bronchi causes deposits in the respiratory tracts, producing suffocative phenomena and threatening death by choking. From the mechanical distribution of the process, however, the other severe symptoms and fatal cases that have nothing to do with suffocation cannot be explained. Here the second factor comes into play, that a severe active poison is produced at the point of action, entering the lymph and blood channels by osmosis and being conveyed by the blood and lymph streams to distant organs and tissues. Löffler in his first studies arrived at the opinion that the bacillus found by him produced a poison, and with this he explained the fact that the bacterium brought about intense general action in the affected or artificially affected organism. He also succeeded in introducing the poison from precipitated glycerin extract of bouillon cultures by alcohol and he was able up to a certain degree to determine

¹ A. Baginsky, Diphtherie und diphtheritischer Croup. Alfred Hölder, Wien, 1898.

experimentally its deleterious effects. The French authors, Roux and Yersin, went further, they discovered that the toxins elaborated from Löffler's bacterium brought about phenomena in animals which were throughout analogous to the severe diphtheritic symptoms in human beings; for example, certain forms of paralysis may be mentioned, the consideration of which we shall enter upon clinically somewhat more minutely. Regarding the nature of this toxin, its probable chemical constitution, its terrible action on the animal organism, these cannot be discussed in detail here; it is sufficient to call attention to the fact that it has been carefully studied, and that especially from these studies the wonderful knowledge of the antitoxic action upon the animal organism developed, which Behring utilized therapeutically in determining the antibodies which were secured from the blood.

Upon the basis of the conclusions which we have reached, it is found that a priori the diphtheritic affections may be divided into two principal groups, first into that group of milder affections in which the author has been successful in limiting the area of the disease and rendering harmless the toxins produced at this point; these are the purely local diphtheritic affections, in which the general action of the poison does not occur. And then the second group, the general constitutional affections, in which the local limitation of the process is not successful, and the further distribution from the point of the first attack is rapid and marked, in which, above all, by the entrance of the toxins into the lymph and blood mass, severe and irreparable disturbances occur in distant organs.

Limited, local diphtheria will always represent the mild, and *general diphtheritic intoxication*, with implication of distant organs, will include severe forms of the disease. By the term **diphtheritis**, the local limitation of the process is meant, by the term **diphtheria** the general involvement of the organism is characterized, and we shall conform to this terminology, which I believe is very proper.

Let us return to the histories of the two cases just quoted. It is not difficult to determine that in both cases we are dealing with forms of local diphtheritis.

The further distribution of the process in the first patient is hardly likely, after the therapeutically protective prohibitive measures used by us, in the other case it may be excluded with certainty. We may expect that in the first case the membranes which are still present will soon loosen, will melt away, similar to the condition which has already occurred in the second case, without any deep lesions, ulcer formation or similar conditions remaining, also without general phenomena appearing later. In fact, these tissues are restored to complete health after a relatively short time, in from three to four to six days. Any one who has the fortune to observe only such cases of diphtheritic disease will hardly believe that the affection with which he is dealing belongs to the most terrible scourges of the human race.

Is there then in any case of a locally appearing diphtheria from the onset the certainty of the local limitation of the process, and with this the fortunate undisturbed course of the disease? As a rule, by no means! During the time, which is now fortunately of the past, in which we were unable to make our patients "toxin-resisting," and to immunize them in time against the local

effects of the poison, we were certain of no case, neither from the later propagation of the process to larynx and trachea, nor from the danger of suffocative phenomena, nor from the appearance of severe later lesions, in particular severe cardiac phenomena, nephritis, and various forms of paralysis which often arose several days after complete sloughing of the membranes from pharynx and tonsils. For this reason the prognosis of the disease was very questionable, even in the apparently mild local forms, and this was true to a greater degree the longer the process continued, and the membranes remained upon the pharynx and tonsils. This has now fortunately become different, since it is possible to immunize the body with the serum of diphtheria if we use it in time and in sufficient quantity. Later, in describing the serum therapy we shall return to this consideration. However, at this place it must not be omitted that even without the action of serum, forms of the disease remaining local have occurred in every, even in very severe epidemics. Here the affected organism was either able itself to produce protective bodies in sufficient amounts or it chanced that the microbes that brought about the local affection were not sufficiently virulent, so that this acute action of the toxins did not occur. However, I should advise not to depend upon such fortunate happenings in any single case; it is well to remember that no case, even though apparently mild, should be trusted.

For this reason an active therapy is necessary in every case, no matter how mild. Generally in these local forms of disease a local therapy will be thought of. This is certainly not unjustified, and we shall learn to recognize a number of remedies which have the effect of combating the local lesion, that are commonly used and are by no means absolutely ineffective, even if they come far short of bringing about what was theoretically expected of them. We could here speak of these therapeutic effects, but I believe it is better to first describe general varieties of the diphtheritic disease and only then to speak of all therapeutic measures in connection.

After having described the mildest local form of the disease, let us turn to the most severe, the **septicemic general affection**. This may be designated as a special division of diphtheria, and I shall describe a case from my former experiences, which, unfortunately, was rich enough in this respect. As a matter of fact, this is a terrible form of the disease, a form which has caused diphtheria to be the terror of entire nations, the specter of annihilation of entire families. Picture to yourself a waxy pale, swollen face, with a hollow glance, semicomatose, with open mouth, shrinking position of the body, the head deeply sunk into a pillow. The nose appears thickened, the nasal openings sore, and a yellowish irritating secretion is slowly seen oozing forth, which irritates the upper lip making it sore, red and thickened. The lips are dry, bloody, fissured. The entire anterior part of the throat appears unevenly thickened, and upon palpation the cervical lymph glands are felt to be enlarged to thick structures, which are not uniformly limited but changed into a general doughy swelling. The child snores, the eyes are half opened, the conjunctivæ are visible, slightly injected, and the angles of the eye usually somewhat purulent. A frightful fetor is noted in the respired air and almost forces us to remain away from the child. The tongue is red, dry, the papillæ standing out prominently. The examination of the mouth, the tongue and

the pharynx causes bleeding, which not infrequently is copious and difficult to control. The entire pharyngeal region presents an appearance which is actually terrible. Greenish-gray to black hemorrhagic masses clothe the pharynx, and nothing more is visible of a normal mucous membrane; the normal pharyngeal structures cannot be recognized. The velum palatinum is markedly thickened, and arising from it, reaching to both sides and anteriorly over the entire hard palate are seen thick, flattened, grayish-black pseudomembranes. Usually the voice of the child is hoarse; the cough which is due to the examination is hoarse, barking; the respiration is somewhat difficult, and, upon inspiration and expiration, slightly impeded without a conspicuous dyspnea being present on this account.

The constitutional symptoms correspond to this terrible picture. Occasionally here and there upon the cutaneous surface, distributed petechiæ are found, or deeper-formed striæ, hemorrhages which are distinguished from the surrounding intensely pale areas by a dark bluish-gray color. The pulse is feeble, can scarcely be felt at all, or is even absent; as a rule, however, it is accelerated, at the same time irregular; the impulse is weak, the heart sounds dull; the belly is edematous; spleen and liver are enlarged; the urine mostly contains albumin; the bowels are constipated, and if a movement is brought about artificially it is of a very dark color and very offensive. The temperature is but slightly raised, scarcely over 100.4° F., occasionally, even subnormal. This is the condition that, as a rule, after two or three days leads to death. In the rare cases in which these septic forms of the disease terminate in recovery, this occurs by ulcerative sloughing of the gangrenous masses and a gradual cleansing of the many deep ulcers produced by this and not without severe general phenomena on the part of the heart, the kidneys and the nervous system, which we shall describe more in detail later on. Weeks and months may pass before such patients recover, and in some cases a persistent damage to the heart remains, which may still be noticeable for years and bring about the early death of the child.

Let us examine the anatomical changes which are met with in autopsy of these severe cases. The pharyngeal structures show the picture of severe gangrene; deep into the mucous membrane a grayish-black coagulated and decomposed mass forces its way; the tonsils have almost disappeared, the deformed structures of the pharynx are scarcely recognizable; and over the thickened, tumorous epiglottis the same smeary grayish-black or greenish masses enter the larynx, leaving but portions of the true and false vocal cords recognizable. Below the arytenoid cartilage and the cricoid cartilage, looking into the trachea, over the dark red, here and there hemorrhagic mucous membrane, fine fatty structures representing thin membranes are noted, which fluctuate under a stream of water. The lungs are hyperemic, partly atelectatic, partly filled with bronchopneumonic infiltrates. The liver is large and soft, the parenchyma is cloudy; the spleen is also large, cloudy, less consistent, of a grayish, dull appearance, and upon the cut surface the follicles are hardly recognizable. In some cases special changes are shown by the stomach; the swollen and thickened mucous membranes show distributed, deep, dark brownish, hemorrhagic deposits in striæ form, radiating from the cardia, and grayish-yellow deposits are noted in the centre of these striæ, which deeply

penetrate into the hemorrhagic areas; occasionally the same changes are noted in the intestinal canal, as a usual thing Peyer's plaques are enlarged as in enteric fever, stand out prominently, are injected and even here and there hemorrhagic, or even ulcerated. An ugly gray cloudy appearance is noted in the musculature of the entire flaccid and dilated heart. There are also cases in which fresh coagula, which are adherent, apparently having arisen during life, can still be noted between the trabeculæ of the auricle or of the ventricle. All in all a typical picture of septic changes. The bacteriological examination of the fresh organs at autopsy allows us to cultivate the Löffler bacillus usually in combination with the streptococcus, whereas from the necrotic portions of the pharynx a rare mixture of bacteria is grown, among which the Löffler bacillus is naturally predominant. We see, therefore, in this form of disease, besides the terrible action of the toxins of the bacillus in the region of its primary attack such as pharynx and nose, the phenomena of the general action of the virus in all organs, which may be recognized as the usual process, damaging the tissues in a most deleterious manner.

The question has been much discussed, whether in the cases described, the Löffler bacillus is the actual cause of these terrible changes or whether this action may be attributed to other microbes. The symbiosis with dangerous streptococci is certainly calculated to increase the virulence of the bacillus, nevertheless, there are enough cases to be observed in which in these changes the Löffler bacillus occurs in almost pure culture, so that, without doubt the most malignant lesions may be due to it alone. For this reason the designation of these malignant septic forms as *Diphthérie à Streptococque*, which appears to be a favorite with French physicians, is not quite correct, it does not even require the presence of streptococci to bring about even the severest pathological phenomena; a high grade of virulence of Löffler's bacillus is alone sufficient, and for this reason this microorganism dominates this as well as the previously described pathological picture.

Between this terrible affection and the previously described mild local forms, lie the other cases of *diphtheritic general affection*. Naturally, with serum therapy, as has already been mentioned, the clinical picture and course of the disease has changed so much that we only meet with these severe forms in cases that come under treatment very late, in which the virulence of the bacillus has been able to attain its full action. It will be well to look at the clinical history of some cases to illustrate this.

Girl aged ten, taken ill eight days ago, showed lassitude, anorexia, and symptoms of general malaise. Four days ago she began to complain of throat pains, enlargement of glands noted on both sides of the neck; the child began to have a fetid breath, and evidently had high fever. Admitted to the hospital without having been treated by a physician. On admission, the first glance shows that we are dealing with a severely ill child. The face is pale, somewhat puffy. The sub-maxillary region swollen upon both sides. The glance is feeble, the entire musculature flaccid, the mind is clear; the voice is not hoarse, but only sounds suppressed, pharyngeal; the lips are dry, fissured. The tip of the tongue is dry, the superficial surface is covered with a grayish coating; the mucous membrane of the mouth is generally dry, only tough, pappy mucus adheres between the tongue and the palate. A serious picture is presented by the pharyngeal region. Both tonsils, the velum of the palate and the uvula are transformed into a greenish-gray thick pseudo-membranous mass. The uvula hangs like a rigid lump of

a greenish-gray color upon the dorsum of the tongue; the enlarged tonsils almost meet in the median line, so that it is easy to understand the suppressed tone of the voice and the somewhat prolonged pharyngeal inspiratory murmur which is present. The gray membranous masses reach almost to the middle of the hard palate. The respiration is not actually hindered, but still it is irregular, about 20 to 25 respirations per minute. The pulse is bad, the wave low, the tension slight, 120 per minute. The cardiac sounds are very weak, dull; the size of the heart is normal in so far as can be ascertained by percussion, although the heart appears to be covered by the pulmonary borders. The temperature is 102.2° F. The urine contains much albumin; it also contains morphotic elements, cellular, somewhat decomposed substances and parts of casts. The rest of the organs show nothing abnormal.

This represents one of the severe cases of *general diphtheritic infection*.

Now let us observe the course which the disease ran in such cases, as a rule, during the period when we were not as yet in possession of a specific remedy, and which it may even pursue to-day if the remedy is only applied eight days after the beginning of the case, and its favorable action is not attained. Mostly, or at least in many such cases, the process which was present in the pharynx rapidly led to gangrene and the complete picture of sepsis developed, which we have described previously. Then the children sank more and more into a comatose condition and succumbed under the phenomena of adynamia and cardiac collapse. With this the fever need not rise to high temperature ranges, nor need special complications develop. Or, and this is the better or the only course of the disease, the children began to improve, the pulse became better, and the albuminuria diminished; simultaneously, a reactive inflammation occurred in the pharynx, which prevented the membranes from spreading and produced desquamation at the margins of the pseudo-membranes. This gradually caused the membranes to loosen by disintegration, and after three to four to six days it could be noted that the pharynx had become free, the swelling had diminished, the red mucous membrane of the velum and the tonsils again appearing. With this, the entire condition of the child had improved; the lips no longer were so fissured, the tongue no longer so dry as formerly, the fever had declined. Convalescence began and uninterruptedly ran its course.

However, this was the rarer case. More frequently, only during this time, those threatening and dangerous morbid phenomena occurred which pointed to severe damage to internal organs, the heart, the kidneys and the nervous system. What characterizes the course of these diseases now since we have employed serum treatment is this, that what was previously the exception is now the rule, that, usually, with the desquamation of the pharyngeal coatings, the decrease of the swelling of the mucous membrane occurs, and with it complete euphoria. Naturally, only then if not too long a period intervenes between the onset of the disease and the employment of the remedy.

Still a third course is open to these cases, i. e., the further distribution of the pseudo-membranous masses to the larynx and trachea, and with severe suffocation threatening life, the phenomena of *diphtheritic croup* appear, which require prompt surgical interference.

All of these methods of termination we shall now have to study. They may be studied in those cases which, although treated with curative serum, did not remain free from *complications*, because the employment of the remedy was too late or it was used in insufficient amounts.

This can be studied from case histories in which **diphtheritic cardiac symptoms** are very characteristically shown as the expression of a *lesion of the heart*.

Girl aged four years; upon the fourth day of her disease became markedly worse and was brought to the hospital. The child was well nourished but was cyanotic from

the onset. The voice was clear, not hoarse, dyspnea was not present. The pulse was small and easily compressible, 138 beats per minute, the temperature was 101.8° F. Small quantities of a mucoid secretion flowed from the nose. The pharynx was markedly swollen, the vault of the pharynx, uvula, tonsils and posterior pharyngeal wall were completely covered by a smeary, gray, quite thick, pseudo-membranous mass; there was fetor exore that was quite unpleasant. The heart showed nothing abnormal; especially were the heart sounds clear. Lungs normal. The urine was of acid reaction, contained moderate quantities of albumin, and showed, among morphotic constituents, swollen and partly degenerated, granular as well as epithelial cells, containing fat granules, also hyaline casts covered by cells and granules. The further course of the affection was completely free from fever, the membranes loosened slowly. During the entire time, in spite of the apparent euphoria, it was conspicuous that a certain coolness of the extremities was present, with a small, easily compressible pulse, varying between 118 and 140 beats per minute. Upon the eleventh day of the disease a slight paralysis of the velum of the palate was noticed, and, apart from the somewhat nasal voice which still existed for some time, was easily recognized by the fact that fluids that were taken easily caused paroxysms of coughing and choking and were also regurgitated through the nose. In the meantime the heart-sounds had become peculiarly dull, and it was noticed in the radial pulse that an intermission of some beats occurred from time to time, this giving the pulse a certain degree of arrhythmia. Up to this time the albumin had not entirely disappeared from the urine. If the heart in this stage is examined it will be noticed that the impulse is weak, scarcely to be felt, percussion of the borders of the heart is not changed, but auscultation shows a peculiar character of the heart sounds which has been designated galloping rhythm. This is a peculiar beat of the heart showing three beats, not always with the same accentuation of the sounds, usually so that the principal accent occurs upon the first sound, but also that the second among the three beats, therefore, the middle tone, is principally accentuated. This peculiar rhythm appears to arise in that the ventricular contraction occurs in two different periods; it is especially then a certain sign of severe disturbance of cardiac action and weakness of the heart muscle if it is not quite rhythmical. This phenomenon is always very important and requires the greatest attention, as it not rarely indicates beginning destruction of the heart muscle, perhaps also of the *cardiac ganglia*, and is thus the first sign of a beginning fatal issue due to the heart. Fortunately, this is not always the case, and in the history just quoted it is possible that the little patient will recover and go on to complete convalescence.

However, we must not conceal the fact that the condition is very dangerous, especially if we recollect the sad results which under similar conditions have occurred too frequently. Under like circumstances, as in the case just quoted, **cardiac death** has occurred, it being impossible to prevent this issue. It may take place in two different ways: In the midst of apparent euphoria, suddenly vomiting may occur and a very serious condition of collapse take place, which rapidly and quite suddenly leads to death; then the pulse disappears suddenly from the radial artery, the child becomes remarkably cyanotic, and later on pale. The extremities, the tip of the nose, are cold; the respiration irregular and may become stertorous, and in spite of all analeptics, the child dies in the arms of the nurse. Or death due to the heart may occur slowly, but is just as certain, in that varying collapse-like conditions and the adynamic phenomena finally increase. In the latter case paralyzes are usually present and the kidneys are affected; with vomiting, difficulty in respiration, severe abdominal pains occur. The lips are pale and cyanotic. The extremities are cold, the pulse can scarcely be felt, thready. The cardiac impulse is weak, minimal, tachycardia is present, so that up to 200 rapid and irregular contractions occur in a minute; or the cardiac contraction becomes increasingly more sluggish and slower, 36 to 40 beats in a minute. Vomiting occurs more frequently, briefer pauses of improvement intervening, which give fresh hope. However, the collapse phenomena return, simultaneously the liver enlarges, becoming larger and larger, and may be palpated as a large stone-hard tumor, reaching down into the pelvis. The child has become apathetic to the highest degree, the eyes have a glassy look, the tongue and the tip of the nose have become cold; respiration is weak, scarcely perceptible. Tired, exhausted almost to the point

of death, sometimes with a completely clear mind, it turns upon the side and gently slumbers without producing a sound, never to awaken again. Involuntarily, even if it were not known, the physician and all those surrounding the patient recognize the action of a terrible poison, which apparently has shown its action by paralyzing the heart muscle.

If we ask ourselves what anatomical changes the heart muscle in these conditions and processes has suffered, we would be greatly mistaken if we assumed that they are always very marked or constantly of the same nature. Occasionally, in fact, nothing is found which could at all explain the loss in the action of the heart, and this is especially the case if death has occurred quite rapidly. In these cases, probably lesions of the cardiac nerves and ganglia arise, which can only be demonstrated with the greatest difficulty. On the other hand, however, there is found, especially in those cases in which the agony has lasted for some time, and in which improved conditions have varied with renewed collapse, the grossest changes in the heart muscle, fatty degeneration of the almost complete muscular structure, gross changes in the nuclei of the muscles, and complete fragmentation or hemorrhagic dissemination of the muscular tissue and with this adhering thrombi which have most probably occurred during life.

But it is not the heart alone that is endangered; the **kidneys** are no less affected, as may be noted from the appearance of marked albuminuria and the morphotic constituents in the urine. It is well known that scarcely any case of severe diphtheritic infection runs its course without pathological implication of the kidneys, so that, for example, Aufrecht has reached the conviction that the disease of the kidneys and the plugging of the uriniferous tubules by shreds of tissue, as the result of parenchymatous changes, represent the primary condition of the severe symptom-complex, the heart being simultaneously affected. This may be true of a number of cases, but certainly not of all of them, as the renal affection and the cardiac implication may run their course independently of each other, a condition that I have observed in numerous cases. In this we must certainly agree with Aufrecht that the severest cases are mostly those in which cardiac phenomena simultaneously run their course with pathologic urinary changes, and that the presence of large quantities of albumin in the urine, and, above all, the finding of certain morphotic constituents, makes the prognosis of the cases decidedly more unfavorable. The presence of numerous peculiar, coarsely granular, changed, refractive, decomposed epithelial, cell masses in the urine for a long time has been the sign of an especially unfavorable prognosis. We hardly know what to think when these severe diphtheritic renal changes, which were described long *prior* to the introduction of serum therapy, are now ascribed to the employment of serum.

The renal affection also shows itself clinically by a diminution in the amount of urine and is especially characterized in that but few, individual cases excepted, marked *renal hemorrhages* occur in diphtheritic affection, in contrast to the renal inflammations occurring in scarlatina, in which the occurrence of blood in the urine is one of the most important clinical manifestations of the disease. The diphtheritic renal affection is further characterized by the *very rare occurrence of dropsy and the uremic symptom-complex*.

The latter condition probably does not arise, in that in severe forms of diphtheria which have not received proper treatment the deadly toxins of the organism caused by the diphtheritic virus develop more rapidly than the picture of uremia with convulsions and coma.

The anatomical changes which are the foundation of the clinical symptoms of the renal condition have been carefully studied and it has been shown that they are due to a true toxic destruction of the kidney in which the macroscopical finding varies greatly. Sometimes the kidneys are hyperemic, enlarged and soft, at other times they are anemic, or the hyperemia is limited to the medullary substance which may assume a bluish-black appearance; often a moderate distribution of the cortical substance, with a reddish-gray or more grayish-white or finally yellowish discoloration of the same is noted. Microscopically, all stages of degenerative change of the epithelia, cloudy swelling, vacuolar degeneration, necrosis and fatty degeneration is seen in the kidney, so that the nuclear staining property in many areas has been completely lost. What is especially conspicuous, in contrast to the scarlatinal renal changes, is the *focal necrosis* of the epithelia. There are also found, peculiar net-like mass-arrangements of colloid substances in the region of the urinary tubules, thickening and proliferation of the epithelium of Bowman's capsule and loss and disappearance of the glomerular loops, so that, in fact, all portions of the tissue of the kidney are implicated in the malignant process.

We have thus seen two organs affected in a deleterious manner by the influence of the diphtheritic virus, but we still meet certain phenomena in the clinical picture which cause us to devote some attention to a third organ, to *the nervous system*.

In the clinical history just communicated, we have already met with a peculiar paralysis of the velum of the palate and a paralysis of deglutition. I shall relate the history of another little patient aged four years, that showed the phenomena of **diphtheritic paralysis** to a much greater extent than the one whose history was previously related.

The child is treated upon the fourth day of the disease, but already shows a very markedly developed laryngeal stenosis, widely distributed diphtheritic coating of the entire pharynx, tonsils, uvula, and velum palatinum. The child, that had high fever, shortly after admission, had to be intubated, simultaneously after 3,000 antitoxin units of Behring's curative serum had been employed. The course was not favorable in the first days of observation, as a distressing cough constantly forced the tube out and intubation had to be repeated several times; the fever also continued, with temperature between 100.4° F. and 102.2° F., with quite a rapid pulse, up to 150 beats per minute. Marked fetor was present in the child from the onset, and the loosening and destruction of the membrane occurred but slowly and with great difficulty; severe diphtheritic rhinitis, otitis media, with a purulent flow, bronchopneumonic symptoms, complicated the clinical picture; with this there was albuminuria and the signs of cardiac weakness, the latter showing itself with a poor and weak pulse. In this case, as in the other, upon the eleventh day of observation in the hospital, the *first signs of paralysis* appeared in the form of *difficulty in deglutition*. Fluid produced cough, and was regurgitated from the nose; at the same time marked diminution of the patellar reflex appeared.

These phenomena developed further and the difficulty in deglutition, simultaneously with newly appearing marked phenomena of *stenosis of the larynx*, compelled us, finally, to desist from renewing intubation, and to perform tracheotomy. After that the fluid could no longer be swallowed, the little patient was nourished three or four times daily with the stomach tube. The following was then noted: The child was very weak; there was still quite high fever, and the lungs were not quite free, showing the seat of bronchopneumonic areas. Above all, upon observing the child closely, it is noted that the angle of the mouth on both sides droops flaccidly, which gives the face a peculiarly relaxed expression; apparently both *facial nerves* are paralyzed, and with this there is bilateral ptosis, somewhat more marked on the right side than upon the left, and the pupils will not respond to light; apparently bilateral oculo-motor paralysis is present. Whether both sixth nerves are paralyzed cannot be determined, as the child does not clearly perceive light. Further, the velum of the palate is rigid; the difficulty in deglutition has already been referred to. If an attempt is made to raise the child to a sitting posture it collapses so that a well-developed *paralysis of the extensor muscles of the back* must be assumed. The abdominal reflexes are absent, as well as the patella tendon reflex and the phenomenon of the Achillo-tendon. What is, however, more conspicuous than anything else is the peculiar, helpless manner of coughing, and the difficult, hindered respiration, although the cannula is quite free, this is due apparently to an *insufficiency of the entire musculature of respiration* including the *diaphragm*. How dangerous this serious condition of the poor patient is, need scarcely be emphasized. It is evident that death may occur at any moment by suffocation caused by *paralysis of the muscles of respiration*, to which cardiac paralysis may be very readily added. Fortunately, these very well distributed paralyses are rare, they were even rare prior to the employment of serum treatment; since the introduction of the same, cases of *paralysis of this extent are quite exceptional*, and in the last few years, as far as my experience extends, this is the only case of the kind that I have noticed.

Let us continue the discussion of these forms of paralysis.

Two principal groups may be differentiated: First, the *early paralyses*, which are almost always seen in the severest, usually in the septic cases, or in morbid conditions which are closely allied to sepsis. The paralysis always begins in the velum of the palate, and is accompanied by prostration of the entire organism, and severe adynamic-cardiac conditions. The cases are mostly fatal. The second group includes the *late paralyses*, which have also been designated as *post-diphtheritic*. These occur two to three weeks, even five to six weeks after the onset of the diphtheritic affection. Here also the paralysis begins mostly in the velum of the palate so that speech becomes nasal and deglutition difficult; nevertheless, frequently as a first phenomenon, the absence of the patella reflex is noted, occasionally after an increase had existed some days previously. From this point the paralyses advance with a certain irregularity, however, in the manner that paralysis of the eye-muscles, paralysis of accommodation, also frequently facial paralysis arise relatively frequently, whereas paralysis of the musculature of the trunk and even of the respiratory muscles, especially of the diaphragm, belong to the rarest forms

of paralysis. Excellent descriptions of these forms of paralysis are found in medical literature; there are the communications of Maingault, Donders, Duchenne, above all, the excellent self-observation of Hansemann, perhaps also the collection of the observations made by myself in my book that has been frequently quoted. The paralysis may also include the sensory nerves, so that *anesthesia* and *paresthesia* may accompany the motor paralysis: *the sympathetic system* may also be affected so that paralysis of the musculature of the intestines and bladder may be observed.

The anatomical basis of these paralyses is formed partly by neuritic changes in the peripheral nerves (*toxic neuritis*), partly they may be due to central processes. Severe anatomical lesions of the ganglia have lately been described on several occasions. I should not like to enter upon a discussion of these conditions as they have not as yet been definitely settled.

Still a special variety of paralysis should be mentioned which has actually nothing to do with the post-diphtheritic paralysis and is rarely observed, but which should, nevertheless, be recognized, these are *hemiplegic paralyses*.

We have had an opportunity of noting three such cases. The paralysis may occur suddenly and may throughout take on the character of an apoplectic attack; it is of a well developed hemiplegic character. As an anatomical basis, an embolic affection in the corpus striatum or also a circumscribed hemorrhagic encephalitis has been determined. Here, therefore, the point of origin is not the nervous system but the vascular system. Apparently at one time the expression of the severe alteration of the blood mass by toxic substances circulating in the blood, that give rise to coagulation and, further, the adynamia of the cardiac action which goes hand in hand with the destruction of the heart muscle, which, finally, causes clot-formation in the heart or in the vessels.

We have now learned to recognize serious changes of organs which are due to the toxic substances which have entered the circulation that are produced by Löffler's bacillus, however, we dare not close our eyes to other affections which, although they are not specifically peculiar to diphtheria, nevertheless, are of the greatest importance to the entire course of the disease. To this the *bronchopneumonias* must be mentioned which accompany the difficult pharyngeal affections, also *intestinal disease* with malignant *diarrhea*, further, the *phlegmonous lymphadenitis* of the neck, *otitis media purulenta*, occasionally with an implication of the bone of the mastoid process and even of the internal ear; further, *secondary peritracheal abscesses*, abscesses of the mediastinum, etc.; they have all been observed by us, they all may have contributed toward bringing about the fatal issue to the toxically influenced and severely implicated organism. We cannot at this place enter more fully into these **complications**. With proper treatment instituted at the right time, they will be but rarely observed.

We must, however, acquaint ourselves minutely with the very frequent and very readily appearing *implication of the upper air passages*, the nose, the larynx, the trachea and the bronchi in the diphtheritic process, and the *suffocative phenomena*, the phenomena of *diphtheritic croup*, which are due to this implication. I have already called attention to the **diphtheritic disease of the nose** in some of the case histories that I have related; I have also

described an ugly, sero-fluid secretion, which, as I said, excoriates the upper lip, making it sore and causing swelling. If the nose is more carefully examined in such cases pseudo-membranous coatings of the exact anatomical character of true diphtheritic membrane are met with anteriorly in the neighborhood of the nasal openings; however, if this is not the case the process may, nevertheless, be designated as diphtheritic, as the secretion contains the diphtheria bacillus in plentiful amounts. This may be determined by a simple dry preparation, and in cases in which the investigation is negative, a culture will decide in a few hours. It should be constantly borne in mind that every light-yellow, fluid, irritating nasal secretion which excoriates the margins of the nose and the lips is suspicious of diphtheria; these phenomena should be borne in mind; then it will not occur as it has so often with physicians, that after this condition has been present for some days and the affection has been looked upon as a simple coryza, suddenly they have been surprised by severe suffocative laryngeal symptoms of a croupous nature in children, unfortunately at a time when it was too late to use effective measures, and when even from serum treatment and tracheotomy they could not hope for relief. This is especially the case in small children, in nurslings, and then *latent or larval diphtheria* is spoken of; however, those who understand these conditions see nothing latent or larval in them.

At this point I shall mention those forms of *pseudo-membranous rhinitis* in which croup membranes line the entire nasal cavity, so that they may be removed in large pieces with a syringe or forceps. For the most part they run a more chronic course, and this morbid process only rarely or scarcely ever implicates the pharynx or even the larynx, and, nevertheless, in these membranes and in the nasal secretions, Löffler bacilli have been repeatedly demonstrated. Apparently, in this instance the condition is due to a *much less virulent form of disease*, which runs a subacute or chronic course, being purely local; nevertheless, I should like to insist on the need of care even here, and the exercise of all the caution in prophylaxis and therapy usual in the case of true diphtheria so as not to be surprised by more serious developments. It is well known that Cadet de Gassicourt has described similar, more chronic, local diphtheritic affections also in the pharynx, and we have had an opportunity of seeing them frequently, even some years since. Not very rarely diphtheria begins, and at that in its severest form, with an affection of the nose, and prior to the period of serum therapy the not quite unjustified assumption was prevalent that particularly these varieties of the disease were the most dangerous. This naturally does not always happen now, although it is true that the septic forms of diphtheria also for the most part implicate the nose.

By far the most dangerous symptoms are those which arise from the *larynx*, and every physician who is familiar with the **true croupous diphtheritic laryngeal** symptoms will certainly, no matter how experienced, feel anxiety if these symptoms appear in a child under treatment, or increase in severity. The most marked characteristic of this form of the disease is *hoarseness of the voice*, the *barking*, dry, hoarse *cough*, and the long-drawn, almost hissing or sawing, *inspiratory and expiratory respiratory murmur*. It is certainly not always necessary, even if true diphtheritic membranes are detected in the

pharynx, to assume diphtheritic disease of the larynx on account of the hoarse voice and barking cough, for these phenomena may also occur in catarrhal laryngitis; it is a well known fact that a very acute catarrhal laryngitis occurs where there is no sign of diphtheritic disease, and with the same symptoms, without seriously threatening the life of the affected child by suffocation, and for this reason the name *pseudo-croup* has been given to the condition. Nevertheless, we will have every reason to look upon hoarseness in a well-defined diphtheritic laryngeal affection with the greatest suspicion and care, and, even in those cases where the pharynx is found completely free, it is considered good practice, either by bacteriological cultural investigation of the laryngeal and pharyngeal mucous membranes or by laryngoscopic examination, to determine that the larynx is free of pseudo-membranes; for there are cases enough in which the formation upon the tonsils and pharyngeal mucous membrane is only slight or in which the pseudo-membranous masses have entirely disappeared from these areas, only then the actual diphtheritic laryngitis appearing. As a rule, diphtheritic laryngitis begins in a period when pseudo-membranes are still demonstrable in the pharynx, so that the laryngitis arises as a result of the descent of the pseudo-membranes from the pharynx to the larynx, and Bretonneau has spoken of these downflowing masses. If the diphtheritic laryngitis develops slowly, the voice gradually becomes hoarse and there is heard, besides, a rough scraping tone accompanying the inspiratory prolongation of the respiration, a less prolonged audible expiration. As a rule, the children have fever, which occasionally reaches high ranges, and now in a relatively brief time, the affection develops more and more to the clinical picture which I shall describe in the following clinical history.

Small boy, aged two, taken ill five days previous. It was noted that the boy was well nourished, but, nevertheless, his appearance upon admission showed that he was very ill. The face had an anxious expression; the eyes were widely opened, the alæ of the nose dilated with each respiration during which the mouth was open; simultaneously we noted that with each of the long piping, hissing, respiratory movements the jugular vein became more prominent, also that the thorax, with the assistance of all the inspiratory muscles, the sterno-cleido, and the pectoral muscles, was markedly raised; we also noted how, upon inspiration, the intercostal spaces were drawn in, a deep furrow forming at the lower border of the thorax, the scrobiculus cordis sinking in deeply and great dyspnea being present. Apparently, there was not sufficient air in the lungs, so that the intercostal spaces and the other soft parts surrounding the thorax sank in on account of the external pressure of air. We noted the sawing, prolonged inspiration, and the hoarse, creaking, barking tone of the cough; with this there was complete aphonia. A glance into the pharynx by no means showed very extended membranes, we were only able to recognize upon the swollen tonsils some grayish-yellow spots and streaks and similar ones perhaps somewhat thicker upon the posterior mucous membrane of the pharyngeal wall. Nevertheless, we could not doubt that we were dealing with *true diphtheritic croup* and it was necessary to relieve the respiratory difficulty, and that as rapidly as possible. In the first place we noted the anxiety of the child, and then the tense radial artery, the hard pulse, the cyanotic condition of the lips, and also the somewhat livid color of the face, these showing us that the child was nigh unto suffocation and required speedy help. We *intubated* at once, but we had everything in readiness for *tracheotomy* in the case of this small child, meaning immediately to proceed to tracheotomy in case of failure of the intubation.

What would have happened to this child if we had not relieved it in the manner we have just indicated? Without doubt, the dyspnea would have in-

creased, the respiration would have become deeper and more labored, and, assuredly, we should have seen the child tortured with the terrible phenomena of suffocation, raising itself as much as its strength would allow, fighting for air, with a livid, cyanotic face, blue lips, covered with perspiration, with cold, moist extremities. Perhaps under the influence of these very great exertions the respiration might have quieted itself somewhat; it would have become somewhat freer if the child had succeeded in bringing up some mucus or even some shreds of membrane with the severe coughing. Then the child would have collapsed in its bed and slumbered for a brief time; soon, however, the attacks of suffocation would have repeated themselves and the same phenomena would have returned, but not for a long time. The powers are weakened; the child now remains quiet, in apparent slumber, longer and longer, the lips and the color of the body become more bluish, the respiration apparently becomes freer, less audible, less sawing and hissing, the cough desists completely; however, if we examine accurately, we note only a very superficial, no longer complete respiration. The mind is apparently no longer free, the child is in a comatose condition, from which it no longer awakens, but slowly slumbers into the condition from which there is no awakening. This would be the infallible, unalterable termination which, according to our experience, neither internal nor external remedies would be able to ward off. And because we knew this we did not hesitate one moment to interfere.

And the cause of this terrible onward course? A glance into the jars containing anatomical preparations of pseudo-membranes in the larynx is sufficient to explain this. It will be noted how a thick pseudo-membranous mass plasters the entire larynx, completely closing the rima glottidis, and how thence a thick, tube-like, formed and compact pseudo-membrane fills the entire trachea, entering through the bronchi, through the smallest and finest bronchioles, even coating them for wide areas. With this it can be seen that the lungs have collapsed, are thickened, and partly, especially around the borders, markedly dilated, resembling emphysema. This is, therefore, the anatomical finding of *diphtheritic croupous laryngo-tracheo-bronchitis*; this dreadful disease is almost invariably fatal, provided we do not succeed in bringing help to the suffering child by means of mechanical and specific remedial measures. Here, therefore, there is added to the toxic infectious process of diphtheria, a mechanical condition which brings about death by suffocation. Now we can understand why the ancient physicians spoke of synanche, garotillo, of stryptsjuka, etc. In fact, of all the dangers of diphtheria that we have learned to recognize up to now, the danger of suffocation, due to the descending croup, is the greatest, and to be all the more feared because it is a daily frequent danger.

Let us devote a few words to some of the clinical peculiarities of the clinical picture of croup.

We have laid stress upon the *aphonia*; this symptom is almost always present, but it may be absent, provided the larynx is free from membrane in the region of the vocal cords, more free than the trachea and the bronchi; therefore, the *presence of the voice by no means excludes diphtheritic croup*; and these cases, as a rule, are the most dangerous because the diphtheritic exudation and necrosis has invaded the parenchyma of the lungs more deeply.

The pulse, further, requires consideration. For some time attention has been paid to this, and especially to the beginning retardation of the pulse, its slowing with the advancing asphyxia, and *pulsus paradoxus* described by Kussmaul; the phenomenon that causes the pulse to disappear more and more during the long-drawn inspiration has been looked upon as a valuable sign. It is not easy to demonstrate this in the restless child that constantly throws itself about; but it may be distinguished if some attention is paid to this point. In cases in which this phenomenon can be noted, a very severe disturbance of respiration may be concluded, and we should keep ourselves in readiness to immediately combat the dyspnea, because the children are threatened by the danger of suffocation. Not so constant are the signs of the disturbance of circulation in the urine, such as the presence of *albumin*, or of blood, or a diminution in the amount of urine. In the moment of greatest danger to life they are not to be accorded too great value.

I have now called attention to the most important phenomena of the diphtheritic process; I have as yet not spoken of the *various localizations of the diphtheritic process at other points*, i. e., the diphtheritic *cutaneous affections* which appear particularly in areas that are the seat of eczema, that belong to the ugliest and most painful forms of disease, as they enter deeply into the skin from the subcutaneous tissue, causing necrosis and leading to sepsis, then, for example, giving rise to the disturbances which have been designated *dermato-myositic*, which bring about an icteroid condition of the muscle fibers and belong to the most serious processes that are observed; further, the *diphtheritic disease of the genitalia*, especially in little girls; they resemble those of the *external auditory meatus* and of the *middle ear* and the *conjunctival sacs*. These severe lesions are noted in widely distributed diphtheria epidemics, especially among a class of the population that live under bad unhygienic conditions. I have as yet not spoken of *mixed infections of diphtheria*, of the serious *combinations of diphtheria with measles, scarlatina, whooping cough* and other diseases. It is readily understood that on account of the toxicity of the diphtheritic process all these combinations are of the most serious import, and prior to the introduction of serum therapy every one of these complications had greatly increased the mortality among sick children.

These conditions have all improved, although we must not conceal the fact that the danger to children, even under the influence of this powerful active remedy still requires the most watchful care and the most profound knowledge.

PROGNOSIS

This leads us to the question of the **prognosis** of the disease. Briefly expressed, every phase of diphtheria, no matter how mild, is to be taken seriously, as well for the patient himself, as also on account of the danger of transmission to those about him. However, we must take into consideration that there are in fact dangerous, and less dangerous epidemics, and that the mortality of the disease is subject to many spontaneous variations. Only, we must not depend upon the mildness of an epidemic in an individual case; this might easily lead to very evil consequences.

In general I may state the following regarding the *prognosis*: *The prognosis is the more unfavorable, the more diffuse the local process, the more the pseudo-membranous deposits cover the entire pharynx, especially distributing themselves to the hard palate, the more smeary the membranes appear, the worse their color and the less localized.* Naturally, the implication of the larynx, with stenotic phenomena renders the prognosis decidedly worse; signs of general sepsis, such as marked fetor, diffuse swelling of the submaxillary and post-cervical lymph glands and, finally, hemorrhages from the pseudo-membranes, hemorrhages from the mouth and nose as well as petechiæ, are calculated to render the prognosis grave. *With all these phenomena the prognosis becomes the worse, the later the proper antitoxin serum therapy is employed after the onset of the affection.*

That the prognosis has become entirely different since the introduction of serum therapy, which has been so frequently mentioned by me, and that by means of this remedy we have obtained a factor which ensures certainty beyond our wildest hopes in prophylaxis and in the therapy of the disease, will already have been recognized from my previous remarks. This subject will be entered upon more in detail later.

DIAGNOSIS

First I shall devote a little attention to the diagnosis of the disease. We might expect that in a disease which is so characteristically developed as a pseudo-membranous affection of the pharynx or of the pseudo-membranous process in the larynx, running its course with dyspnea and signs of suffocation, the diagnosis could not be mistaken. This is true up to a certain degree, and an experienced practitioner who has cultivated the art of inspection will only rarely fall into error or even be placed in a position of doubt. In fact, the clinical finding of the grayish-yellow, or grayish-green, thick, membranous deposits upon and in the pharyngeal tissues, for the most part decides the diagnosis. How certain this is, may best be seen from the fact that in our hospital the decision of transferring patients into the diphtheria division occurs principally from the clinical findings, and I might say, almost never has a case been looked upon by us as diphtheria and brought into the pavilion in which only diphtheria patients are accepted that was not proven by a later bacteriological investigation to have true diphtheria. Nevertheless, we must not conceal the fact that there are also *obscure cases*, cases of well-developed follicular angina that give rise to doubt, *and these cases require the bacteriological determination of the Löffler bacillus.* The bacteriological examination decides the diagnosis for these cases, which we place in a separate

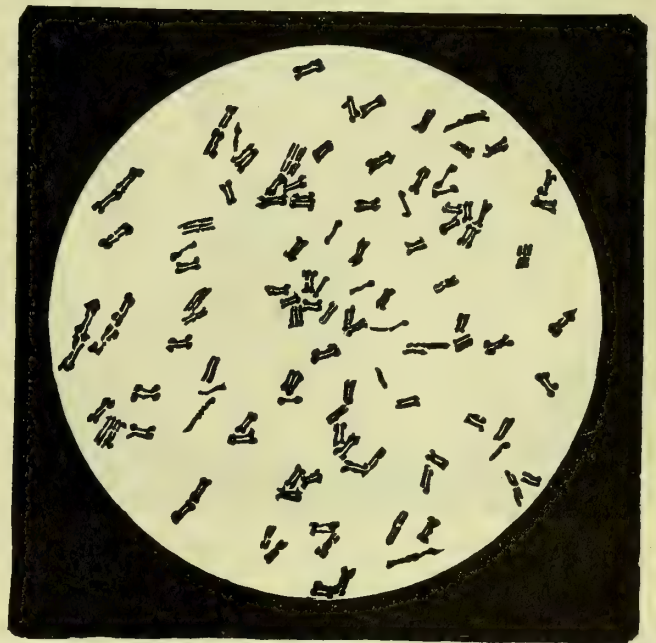


FIG. 34.—PURE CULTURE OF DIPHTHERIA BACILLI.

division. Not as if the presence of diphtheria bacilli without a determinable disease of the pharyngeal membrane or the nasal membrane or of the larynx could and would decide us in favor of the diagnosis of diphtheria, but we may be certain of the fact that apparently healthy persons, also children, may carry diphtheria bacilli around with them. These persons are dangerous to others on account of contagion, *but they are not diphtheria patients themselves*. On the other hand, that individual is affected by diphtheria who has the combination of an angenoid mucous membrane infiltration or even of a pseudo-membranous membrane coating in the nose, in the larynx or in the trachea, in which the Löffler bacillus may be microscopically determined or can be recognized in culture. On the other hand, of those that show similar morbid

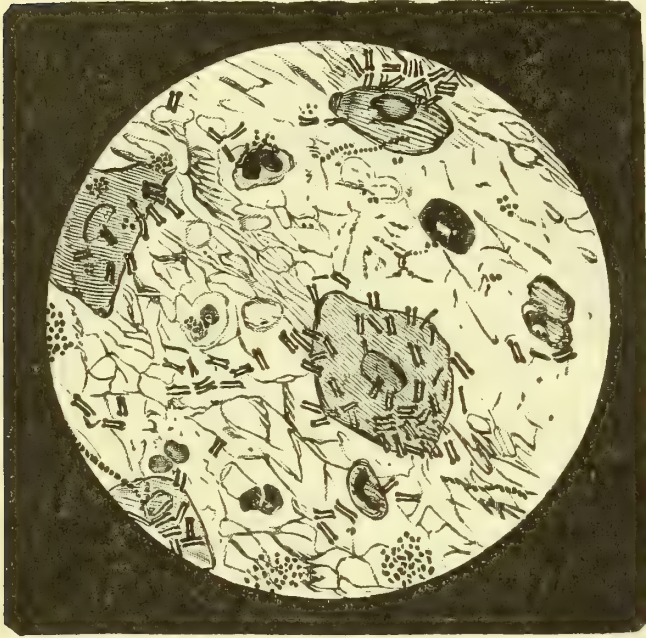


FIG. 35.—A PREPARATION FROM A TONSILLAR MEMBRANE.

(Containing epithelial cells, leukocytes, mucus threads, staphylococci, streptococci, etc., and characteristic diphtheria bacilli.)

conditions, in whom the demonstration of the Löffler bacillus is not possible, it may be declared with great probability, almost certainty, that they are not ill of diphtheria. The course of these latter affections that are mostly due to staphylococci and streptococci is differentiated from the true disease in which the diphtheria bacillus is recognizable. In this, therefore, consists the enormous value of the recognition of the Löffler bacillus, and for this reason it is necessary that the physician should be so thoroughly trained in the determination of the bacillus that it is no longer necessary for him to require the proof from another source, even though it may be necessary to erect laboratories of investigation to aid the busy practitioner. Only the physician must himself be master of

the methods of investigation, for the examination is easy and may be readily carried out by any physician who has the slightest training. It is only necessary by means of forceps, previously rendered sterile, to take from the pharynx a shred of the pseudo-membrane; this should then be washed in boiled or sterile water, stroked upon Löffler's blood serum, which is readily purchasable, 2 or 3 tubes being used, well closed with sterile cotton, and kept in a place at the temperature of the body from five to six hours; even after this time the characteristic growth of Löffler's bacillus may be macroscopically determined, which naturally must be confirmed by the microscopic examination of the dry stain preparation (Fig. 34) to determine the presence of the bacillus by its morphological properties. This can be learned and performed by every practitioner; and if this appears too difficult for him he may at least take directly from the pharynx a small particle of the diphtheritic mass, wash it, smear it upon a cover-glass, allow it to dry, and stain it to determine at once the microscopic picture, therefore, to demonstrate the presence of Löffler's

bacillus without culture (Fig. 35). Naturally, this second method of examination is not as certain as the first, the culture method; but for many, and even for most cases, it is sufficient. Therefore, there can be no error in the diagnosis, it will be impossible to mistake a scarlatinal angina or a follicular tonsillitis for diphtheria, but also, vice versa, the former diseases will not be assumed when actual diphtheria is present, in these cases, to the detriment of the patient, diphtheria being overlooked until too late to treat it with active remedies.

THERAPY

If there be a desire to become familiar with the entire deplorable helplessness of therapeutic procedures in the cure of a disease, then the history of diphtheria should be studied. Apart from *tracheotomy*, which was introduced into the therapy of diphtheritic croup by Bretonneau, Trousseau, and Guersant, and *intubation* first attempted by Bouchut and finally perfected by O'Dwyer to relieve laryngeal stenosis, the entire therapy of diphtheria, which for many hundred years, and even for thousands of years, has been in the hands of physicians, is a complete failure. I may say this, as since the beginning of my professional activity in a large country practice, as well as later in city practice, I have been in constant combat with this terrible disease, and in my hospital for many years, in spite of arrangements for the treatment of disease which could not be surpassed, have had but the most deplorable and discouraging results. Tracheotomy alone excepted, physicians were almost helpless to ameliorate the course of this grave affection. With the best intention to help them, what has not been tried and recommended among local, internal and external remedies in the long years since the more marked reappearance of diphtheria epidemics in the second half of the nineteenth century, with what have not the poor children been tortured! If it were not entirely superfluous, I could report all of these attempts, but it would require pages, and the sum of it all would be—that everything was futile! Even after the discovery of Löffler's bacillus and of its toxins, when professional endeavors were actively directed toward neutralizing the bacillus in the human organism, I said—it is worth while to take a retrospective view of this kind—in a communication that appeared in the year 1892 regarding my therapeutic attempts: "Whether we look upon the diphtheria toxin as a toxalbumin, as an enzyme, or as another kind of chemical body which is produced in the organism itself, at the present time it displays an action which cannot be controlled because we possess no remedy to combat it." And then followed the enumeration of those methods and remedial agents which we have tried in vain. During this period of completely recognized helplessness, Behring made his discovery regarding the antitoxic action of serum of animals poisoned by diphtheria. After our former experiences, how skeptically the discovery of Behring was regarded may well be imagined. Step by step, however, our doubts disappeared because of the fortunate results which we, with Dr. Aronson, one of the former assistants of the hospital, attained with an excellent curative serum taken from horses. There followed now, at first tentatively, but with increasing certainty, our communications regarding these fortunate results; I allowed my assistant, at that time Dr. Katz, to report 128 cases at the meeting of the Berlin Medical

Society on June 27, 1894; and then, in the year 1895, after the preceding lively discussion in reference to Hansemann's attacks upon serum therapy, I was able to publish 525 cases.¹ I should not have permitted myself to thus call attention to the development of my own observations, if the overwhelming impression of the curative effect of serum therapy were not brought out in such an instructive manner; this forced the previously skeptic Virchow to remark upon consideration of the figures obtained by us that by these "it was sufficiently proven that the curative serum develops a favorable action"—which I would not even admit if it depended upon the proportion of figures, and our own clinical detailed observations did not confirm it, because, particularly in the judgment of therapeutic results, there is nothing more deceptive than mere figures. I shall have to return to this at a later time. But what still further influenced me to refer to my own observations was the curious and rather conflicting fact that in his publications, apparently with definite purpose, Behring himself ignores the results which were gained at our laboratory, and by this curative agency, and scarcely appears to realize that, in spite of all the great honors which distinguished him, the introduction of his curative serum into practice would not have occurred for a long time if it had not received this support.

Regarding the **curative serum** itself, I may refer to Behring's and Ehrlich's publication, the description of its method of production and the determination of its antitoxic value. We are concerned principally with its method of use. I have published everything that the practical physician should know in my book,² have there also mentioned some of the inconveniences which now and then arise from its use, and shall here only refer briefly to the most important points.

The *quantity* of antitoxin units to be employed in the individual case depends upon three conditions: 1, upon the duration of the disease; 2, upon the severity of the affection; 3, upon the age, that is, the size, of the sick child. Therefore, *the largest dose* will have to be used in the case of an older child which is well developed, of about thirteen years of age, and that has been suffering for about three days with general diphtheritic affection, showing phenomena of stenosis of the larynx. Such a case would require the *employment of 3,000 antitoxin units*. On the other hand, in a young child, for example, about two years of age, upon the first or second day of the disease, provided the general implication of the organism be not too marked, not over 1,000 antitoxin units would be necessary. In general it is well to use the full quantity in one injection, the action of the remedy should not be decreased by dividing the dose. Regarding the necessity of using more antitoxin units than was originally thought to be requisite, the observation that fever is still present upon the second day after the employment of the serum will enable us to decide, provided of course that there are no other causes for this fever than the diphtheritic infection, thus, for instance, an enlargement of the glands, pneumonia, etc. The continuance of the symptoms of laryngo-stenosis or the especially slow loosening of the pseudo-mem-

¹ A. Baginsky, Die Serumtherapie der Diphtherie, Aug. Hirschwald, Berlin, 1895.

² Ibid.

branes, which usually occurs in the first three or four days, *may be the reason for giving another decided dose of 1,000 to 1,500 antitoxin units.* Upon the whole, in the severest cases we have not exceeded *4,000 antitoxin units.* [The most concentrated serum should be employed and care should be taken to procure that made in a well-conducted laboratory and not kept too long in stock.—ED.] The curative serum must naturally be employed with all anti-septic precautions, but scarcely more care is necessary than is required in any other subcutaneous injection. We employ a glass syringe with a butt end of asbestos, and always select the external surface of the thigh as a point of injection. The injection should be given flat, subcutaneously, never too deep, about below the fascia of the muscle and into the muscular tissue. Too deep injections are very readily followed by abscesses.

The action of the remedy is the more intense and more certain the earlier it is used after the onset of the disease; four to five days after the onset of the disease it loses its action in a great number of cases.

This we were always able to observe in our cases, although an absolute certainty can never be acquired from figures and much depends upon the circumstances in the individual case. We may regard the fact as assured, that, with the early application of the remedy, neither laryngo-stenotic phenomena nor septic infection of the organism occur, but that the disease takes on a local non-toxic course soon after defervescence. I must not omit the warning *that the physician should not be too cautious with the dose,* further that he need not fear any *secondary deleterious effects.* All that has been designated by the opponents of serum therapy as evil secondary effects are not to be compared to the extraordinary results of cure, and what may eventually happen is at the most fever lasting two or three days, accompanied with an *urticarial skin affection, occasionally arthritic pains;* however, as I can assure any one from my very large experience, these are without importance and without subsequent damage. Truly, bad accidents, provided they cannot be referred to very special conditions—I once saw a uremic attack in a child following an immunizing serum injection after measles—are exceedingly rare; and in the cases mentioned in literature in which *death occurred* this was due to entirely different causes than the use of serum.

The *favorable action of the remedy* may be seen from the following signs: the decline of the temperature up to complete defervescence, and the euphoria going hand in hand with it; the arrest of the exudative and necrotic process at the local focus of the disease; and, even if not in all, nevertheless, in numerous instances, the retardation of the laryngo-stenotic phenomena. This must not all be expected upon the day of the injection; moreover, not rarely an increase of the local process is still observed, but upon the second and certainly upon the third day, if the amount of the injection has been sufficient an arrest of the process is noted and a demarcating redness surrounds the diphtheritic local focus and the disintegration and loosening of the membranes occurs. The peculiar change in color which the membranes undergo is remarkable; from a grayish-yellow to a grayish-green color, to a more light yellow color, which finally becomes a deep yellow. In many cases, and especially in those in whom the serum treatment has been begun upon the second or third day, the danger is over with this antitoxic action of the serum

and the patients enter upon an obviously increasing improvement, which becomes more noticeable day by day, leading without interruption to complete recovery.

Let us now devote ourselves to the discussion of the **local treatment** which the diphtheritic areas require, besides the serum treatment. Fortunately, all the former mechanical and chemical measures that were employed to remove the diphtheritic membranes, the use of which tortured the children to a dreadful extent, have disappeared from our therapy. If we still employ these measures it is only to destroy the bacillus and to prevent the production of toxins, as the bacillus is not influenced in its propriety of life by the serum. For this purpose, gargles of potassium permanganate (2 to 1,000) or boric acid (3 per cent.) may be employed; or a soft cotton brush may be used to paint upon the parts a 1 to 2,000 solution of corrosive sublimate or a combination of ichthyol 5 per cent. with 1 to 2,000 corrosive sublimate, which is especially valuable as ichthyol kills the cocci that are present, whereas corrosive sublimate only influences the bacillus. Finally, powders that are easily insufflated may be utilized; sozodol in combination with milk of sulphur is best for this purpose.

In how far we are able to retain the toxins which are formed by the Löffler bacillus in a nascent condition at the point of their production, even by submucous antitoxin injections, and to neutralize their first effects, as is proposed by Behring lately, I cannot decide, as our experiences have not been sufficient as yet. Reasoning by analogy from experiments in test tubes and from trials with animals, and from results obtained, it is quite possible that unexpected cures may result from this application of the remedy and it is certainly worth a trial.

Besides the measures already mentioned, we employ ice-bags and administer ice internally, which gives decided relief.

It is hardly necessary to state that the patient must receive good nourishment and that it must be administered with care, in so far as this is possible during the febrile period. Small quantities of wine, perhaps also a cinchona decoction, may be administered to maintain strength, and with this the therapy of uncomplicated cases has been exhausted.

The condition in diphtheritic croup and in the sequelæ previously mentioned is different. Diphtheritic laryngeal stenosis requires, as I have already stated, the operation of **intubation** or **tracheotomy**. I mention intubation first, for, in fact, it is preferable to tracheotomy wherever it can be used. The instrumentarium is well known and I have described the manner in which the operation is performed in my book on Diphtheria very completely, besides the text is illustrated by exact photographs. The patients breathe very freely through the intubated tube. It is true, intubation is not a very easy operation and must be practised. In the hands of an unskilled operator, the intubator armed with the tube is a dangerous instrument which may cause death by producing injuries. If the tube has produced damage the children mostly die of secondary bronchopneumonia. This must be remembered and no one should attempt intubation until after thorough practice upon the cadaver. For this purpose I have had a model made which I keep in the post mortem room, upon which I allow my students to practise. The tube by its weight and by friction,

especially if it remains in place for some time, brings about injuries which are designated tube ulcers, particularly the lower end of the tube causes this.

With all this, the results of *intubation in connection with serum therapy*, are far more favorable than were formerly attained with tracheotomy. In this connection, I may refer not only to the publications of the skilled American physicians, but also to those of Ranke, Bokai and others; we also, in general, have had very good results, so that among 109 cases reported at the Medical Congress at Moscow, of laryngeal stenosis treated by intubation, only 9 = 8.73 per cent. died, and of all laryngeal stenosis 218, 40 = 15.5 per cent., a result which, compared with our former figures, is favorable beyond all expectation. These results, as I frankly admit, might even be better if the dexterity of the operating assistants were perfect, but this can hardly be attained on account of the constant change. From this illustration it can also be seen that mortality figures are dependent upon other causes than the disease itself and the remedies employed to combat it.

Tracheotomy can also, as formerly, be used in laryngeal stenosis, but as it causes a wound which is obviated in the case of intubation, and this wound increases the difficulties and dangers, it has attained a secondary importance and is only utilized in cases that are not suitable for intubation, as in the case of a markedly narrow pharynx, etc. Naturally, the results of tracheotomy, which, as a rule, is only utilized as a secondary operation, are only secondary to those of intubation; thus, in 14 cases of primary tracheotomy, 10 = 71.4 per cent., and in 22, after repeated intubation of secondary tracheotomies, 15 = 68.2 per cent. of fatal cases. Regarding the technique of tracheotomy and the after-treatment, surgical works should be consulted. Proper spray arrangements are also of value in the treatment of diphtheria. One of the most pleasing results of serum treatment is the spontaneous retardation of the stenotic laryngeal symptoms under the action of a properly used spray. Children with symptoms of stenosis of the larynx are allowed to inhale a strong spray of steam for hours, which contains at the most weak solutions of sodium chlorid or a 1 per cent. to 2 per cent. solution of boric acid.

Regarding the **treatment of complications** and *sequels of diphtheria*, we shall first speak of the cardiac affection. Unfortunately, little that is valuable can be said regarding the treatment of cardiac disturbances after they have once become conspicuous. The disturbance of the heart muscle that is due to the toxin of diphtheria can be but slightly influenced therapeutically. All of the heart tonics employed by us, small doses of digitalis, strophanthus, caffein, tincture of the chlorid of iron, etc., have proven unavailing. No remedy has been able to arrest the advancing cardiac death; long rest in bed and good dietetic treatment have shown themselves to be the most valuable remedies in assisting children to withstand this threatening danger. The same is true of nephritis. Careful bland diet, alkaline mineral waters, here and there mild tannin and iron preparations, are almost the only remedies that we employ. Rest and diet act best in this condition, and in summer change of air to a healthy country district is of value. The treatment of other complications, pneumonia, otitis, secondary lymph-gland abscesses, etc., is scarcely different in the case of diphtheria from that arising from other conditions.

In conclusion, a few words regarding **immunization** of children threatened with contagion. In our trials with antitoxin treatment we began at the onset to give prophylactic antitoxin injections to the brothers and sisters of the patients who were brought to us affected by diphtheria, in order to protect them from infection. Fortunately, we were enabled to show in our divisions of the hospital that if by any accident diphtheria were introduced we could always succeed in preventing its dissemination, as was also the case in threatened families. Since then, in a similar manner, immunization has been continued in exposed places and our figures show hundreds protected. Whether, as Behring has lately wished and advised, general immunization of children against diphtheria, similar to vaccination, is to be introduced, or whether it be unnecessary to do this will depend upon the further course of diphtheria epidemics. It is certain that in threatened districts, especially in the country, the further spreading of the disease may be prevented by immunization. On the other hand, in the cases of children that can be well observed and are constantly under the control of physicians, we may content ourselves in employing a sufficient dose of curative serum immediately upon the appearance of the diphtheritic attack. Up to the present our results with serum therapy teach us that early serum treatment is capable of preventing the dangers of the disease. Thus, it will depend perhaps upon the local and social conditions whether the physician is to employ one or the other method of prophylaxis. The dose for immunization purposes varies according to the age and size of the child, between 200 and 300 antitoxin units, only rarely has this dose been increased. As a rule, this has proven sufficient.

I might now close my discussion. I should not like to do this without clearing up a certain point which, unfortunately, serves to bring about a great deal of confusion regarding the value of serum therapy, and thereby incalculable damage to our children, i. e., the application of the statistical method to determine the curative results attained. The **value of statistics** in ascertaining the actual permanence of the processes and circumstances in things and in man is beyond all doubt and incontestible, and the less complicated the relations the more certain and likely will be the results which may be determined from such a compilation, grouping and addition. On the other hand, the scientific and conscientious statistician knows that on account of the complicating circumstances and relations attending figures, the difficulty of their proper estimation grows and the results may be far from the actual truth. What can be more complicated than the course of morbid processes in which certain positive factors as to age, weight, social position, the number of affections, etc., are taken into account, but also innumerable other conditions that cannot be mentioned, even unknown circumstances, such as the constitution of the patient, the nature and virulence of the pathogenic agent, the favorable influence of remedies and of physician, as well as faulty observation and reports, and errors in treatment, may also affect the individual case. This renders professional statistics untrustworthy, and in so far as the most simple relations of figures are not taken into calculation, they are faulty, without value, and harmful. This accounts for the paucity of professional investigations and card index statistics, which scarcely include the simplest and most superficial relations of the investigations, not to mention the details of the

individual morbid process. Only after a very large, almost enormous number of results, which include the omissions and errors of individual numbers, are observed, is a result attained which approximates the truth. This, above all, renders general statistical reports regarding therapeutic results valueless, and so much inferior to the experience of the faithful observer who notes the minutest details. Hence the useless and detrimental controversy with statistically produced small figures regarding the curative properties of serum therapy. Are the conditions of a single region similar to those of another, or is even one case exactly like another, and even in the same places, under the same physicians, persons, conditions, are the morbid processes exactly similar? Do we not even see in this hospital how the severity of the individual case varies, the children coming to us having entirely different constitutions, their disease and a thousand other conditions varying greatly? But just for this reason the observation of an impartial, well-trained physician who watches with open eyes is more valuable than all statistical reports. From this viewpoint, the judgment of serum therapy arising from careful clinical observations of the special case, with all the variations and surrounding conditions, is the only proper one, and the one that comes nearest the truth. This is the reason why we do not turn to the right nor to the left, but singly and alone, holding to our own base of observation, we arrive at our conclusions regarding the curative value of serum therapy and shall even attain better results.

Let me then say again in regard to the results reached by us, as far as human observation is able to judge, that in no disease of man have we attained such a certain remedial agent as is curative serum in the case of diphtheria. This unalterable opinion is based on our own cases in which we have observed even the slightest variation. To us the individual figure is not merely a number but an actually observed case, and for this reason the sum of the numbers does not confuse us. If in one month the mortality figure of 20 per cent. to 30 per cent. results, and in another only from 5 per cent. to 6 per cent., we can tell exactly why the figures could only be such, and why they could not be different. If in one month a greater number of severe septic cases, or children almost *in extremis* are brought to us with laryngeal stenosis, we know that the majority of these children will be lost and that our mortality reports will be more unfavorable, but this has absolutely nothing to do with the curative remedy, at least not unless we ask that means be resorted to in human beings to bring the dead back to life; for, in fact, in those cases, for the most part, we are dealing with patients in whom death is absolutely certain.

If now while taking into consideration all of these conditions, I say that our mortality figures in those cases which are at all susceptible of cure by the application of curative serum have improved in the proportion of three to one, if I say, further, that by judging the disease forms and patients under similar conditions, our mortality from diphtheria has decreased from about 45 to 15 per hundred, this observation regarding the curative property of the serum appears to me to be more valuable than any number of statistical compilations can be. Do not allow yourselves to be confused by sophistries, do not allow yourselves to be deterred by terrible pictures which have been described by

inexperienced persons who have attempted to use serum treatment, do not allow an hour to go by if you are treating diphtheria patients without resorting to this life-saving remedy.

Finally, to acquaint you with our rules, in a few words which should guide you in your therapeutics at the sick bed of diphtheritic children, I shall give the following:

1. Use of the curative serum in sufficient dose as early as practicable, if possible immediately after the onset of the disease, in doubtful cases even before the diagnosis has been determined by a bacteriological examination.

2. Local treatment of the diphtheritic membranes by mild applications or dusting by some of the remedies previously mentioned, without damaging the mucous membrane and without unnecessarily torturing the child.

3. Applications of ice-bags to the neck, and internal use of small pellets of ice.

4. Saving and assisting cardiac power by good and proper nourishment and by absolute rest.

5. Early relief of laryngeal stenosis by intubation or tracheotomy.

6. Proper treatment *lege artis* of complications and sequels.

[See also Serum Therapy, page 909.]

PNEUMONIA

By E. v. LEYDEN, BERLIN

"My physician showed more anxiety in regard to my condition than his professional duty required. He trembled for me and not on account of the honor of his art. He did not content himself merely with prescribing drugs, he administered them with his own hand. He comforted my troubled relatives. During the critical periods he was at my bedside. Nothing was too much for him; the most difficult and most revolting services were as nothing to him. To this man I do not only owe thanks as to a physician, but also as to a friend. How could I ever compensate him for all this?"

L. SENECA, *De beneficiis*, L, vi.

CLINICAL HISTORY

A MAN aged twenty-one, a waiter, admitted to the hospital on October 31st, taken ill the day previous. He entered the Charité in a comatose state. The history showed that upon October 29th he was suddenly attacked with nausea, pain in the chest, having been quite well the day previous. He did not remember having had a chill; there was cough, pain in the chest and fever. As his mind was not quite clear his parents sent him to the hospital.

Status præsens on November 1st: Patient is a well-built man, somewhat thin, moderately good musculature; color of the face is increased due to fever, cheeks slightly cyanotic. He is restless (jactitation), turns toward the left side. Skin is dry, hot, temperature in the morning 102.6° F., pulse 112; the night previous 106.2° F., pulse 120. Respiration markedly increased, 40 to 44, short, apparently painful paroxysms of cough. Expectoration sparse, tough, sticky, glassy, rusty. Patient complains of pain in the chest upon the right side; the day previous these pains were said to have been upon the left side (alternating pleural pain). Patient scarcely responds to questions, he is evidently somnolent; at present no delirium, no tremor. The physical examination of the thorax shows marked dulness upon the right posteriorly, from the middle of the scapula to the base of the chest. In this area intense bronchial breathing and upon coughing crepitant râles. In the right axilla distinct dulness, posteriorly upon the left side increased vesicular breathing, with râles. Cardiac dulness not increased, apex beat inside of the left mamillary line. Heart sounds clear and distinct. Urine dark, turbid, showed a sediment of urates, no albuminuria, no diazo-reaction, feeble urobilin reaction.

A diagnosis of *typical (genuine) pneumonia* was made, hepatization of the right lower lobe upon the fourth day of the disease; somnolence.—Prognosis *vergens ad bonum*.

Upon the ninth day of the disease the temperature of the patient was 99.3° F., pulse 90. Patient was somewhat pale, but quiet and had a natural look. His countenance was cheerful. The patient had passed the crisis and was in such a favorable condition that we had to say—in case unexpected complications should not happen—that he was "through," i. e., out of danger and convalescing. The physician then had the duty, which is not always easy, of guarding the convalescence, with caution and skill, and of regulating nutrition, digestion and sleep so that no decided influences should interrupt the course of convalescence and the patient should regain his previous strength as rapidly as possible.

This is the history of a case of genuine pneumonia running a typical course in which, however, the crisis only occurs upon the ninth day, whereas

this event is most usual between the sixth and seventh days. The fever curve (Fig. 36) shows the course of the disease: The severity of the fever diminishes about the fifth day (morning temperature of 99.3° F.), rises, however, again to 103.2° F., and upon the seventh day shows a remission to 101.1° F. and a second exacerbation of the affection and the fever, which lasts from the seventh to the ninth day, the temperature then rapidly falling to 98.6° F.

The dulness posteriorly upon the right side cleared, soft bronchial breathing and plentiful crepitant râles were present (crepitatio redux). The sputum no longer rusty but lemon-yellow in color and turbid.

In general this presents a mild course, the disease not having required active therapeutic interference. Only one disturbance occurred which required observation, which is not rare, and with a proper treatment almost always runs a favorable course. Upon the fifth day of the disease, the mind

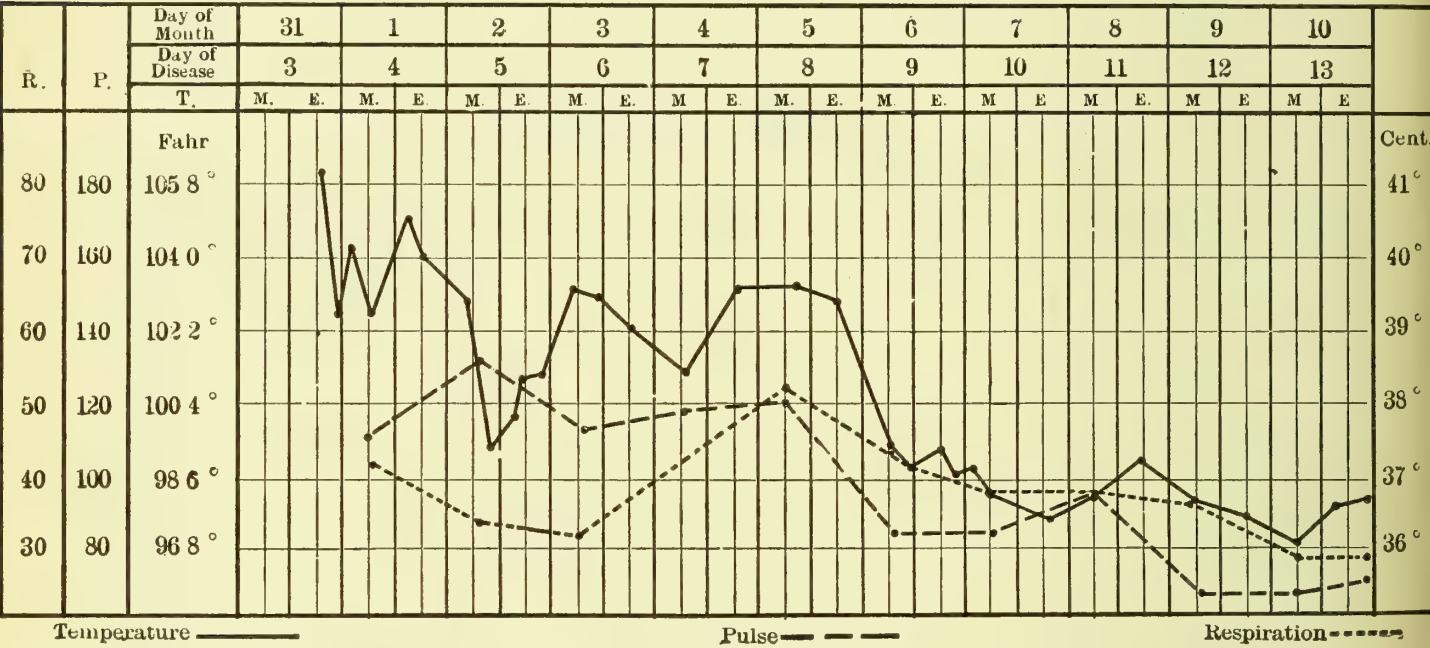


FIG. 36.

was no longer clear, the pulse arose to 130, with this, however, the subjective condition was good. It is to be expected that this delirium will increase, and, at the time of the crisis, may take on a furibund character, not a delirium potatorum, but a *delirium defervescentiæ*, which at the time of crises in acute diseases occurs mostly in youthful individuals and is not without danger!¹ This variety of delirium increases particularly during the night. The patients are restless, jump out of bed, and not rarely even attempt to jump from the window; or they may attack their neighbors. To prevent a condition of this kind, upon the fifth day of the disease, which shows the lowest temperature on the chart, the patient was given a dose of 0.01 morphia; he only slept one hour, awoke, was confused and attempted to jump out of bed, a second dose was injected, when he fell into a quiet sleep which lasted several hours, from which on awakening he was comparatively quiet. Upon this and the following days the patient was confused at times and each night was given an

¹ It is necessary to state that in alcoholics these deliria occurring in defervescence may take on the character of severe delirium tremens.

injection of morphia; after the crisis the mind was perfectly clear. These *epicritical* or *defervescence deliria* disappear as soon as a prolonged, quiet sleep is secured. The treatment consists in administering narcotics and stimulants (alcohol). If the delirium is very severe it may require large doses of morphia or chloral, and two to three days are necessary before sufficient sleep is obtained. This period is by no means without danger. The patient exhausts himself by his restlessness, he emaciates and death may result from collapse or pulmonary edema; or he succumbs to a sudden outbreak of the fever delirium; I have known several instances in which such patients jumped out of the window. I, therefore, advise even upon the first appearance of these deliria to watch the patient carefully. Care is to be observed that he is not left alone for one moment, the windows are to be closed, briefly everyone must be upon his guard! These precautions obviate the danger.

Much severer is the *delirium potatorum* in pneumonia, which occurs preferably about the time of crisis and may be readily recognized by its characteristic symptoms, the alcoholic tremor, the hallucinations of rats and mice, and the picking at the bedclothes. The severity and duration of this delirium, the cardiac asthenia of the alcoholic, presents great danger for the life of the patient. The treatment is along analogous principles: alcohol, nutrition and narcotics; it must be very carefully applied to prevent serious consequences.

For the present, I shall limit myself to these remarks in the treatment of pneumonia. The proper appreciation and treatment of the delirium is a practical and important point. The difficulties in the treatment of pneumonia occur particularly at the time of the crisis; here the greatest attention, insight and experience of the physician are required. The therapy of the preceding days must, in a measure, be a preparation for the crisis, i. e., care must be taken that the patient enters upon the crisis under the most favorable auspices and that he emerges successfully.

I shall say more regarding the therapy of alcohol and other narcotics in the treatment of pneumonia. Formerly the effect of these remedies was feared, a paralyzing action on the heart being ascribed to them, especially to morphia.

Physiological experiments do not give a sufficient proof for such a belief, but, unquestionably, the respiration, as is generally the case in sleep, is slower and weaker, and this may indirectly reflect upon the cardiac activity.

In all cases of dyspnea and cardiac asthenia care must be taken in the administration of these remedies, and we must be particularly cautious if *cyanosis* is present. If to the hebetude of the sensorium, somnolent conditions are added, due to the bacterial toxins, the use of a narcotic is very questionable; after large doses a deep, prolonged sleep may occur, which must be feared as it may readily lead to coma and collapse. However, if coma and collapse are not present, but, on the other hand, there is great fear that the patient may exhaust himself by his restlessness and delirium, then the indication to produce sleep and rest is an imperative, a vital one. It is well to be cautious and small doses of morphia should first be injected (0.005–0.01), and these should be given during the day so that the patient can be watched and it may thus be observed how the remedy is borne; this controls future action.

Injection of morphia has the advantage that the effect occurs quickly and also passes off rapidly; however, the use of chloral and trional (0.5–1.0) is per-

missible. If there is reason for special care and if fever is still present, it is well to begin with antifebrile drugs, which also have a narcotic, quieting action. Antipyrin, phenacetin, salipyrin, or pyramidon are given in doses of 0.5 in the evening or two to three times during the day. In cases of severe delirium we must content ourselves if we succeed in allaying irritation and producing a brief sleep. By and by, from about two to three days, it will be possible to produce quiet sleep after which, usually, the brunt of the affection is passed.

In this connection I shall mention other clinical histories, which I shall briefly describe in pointing out some especially remarkable characteristics, without entering upon typical individualities.

CASE II (Fig. 37).—This patient, R. G., a laborer, aged twenty, fourteen days previous to entering the hospital had a genuine pneumonia. He was admitted to the hospital upon the fifth day of his disease, having a fever of 105.1° F., the physical signs were well developed, pulse 100, high tension, not dicrotic (pulsus magnus), expectoration was tough, glassy, rusty. The face was markedly turgescnt and reddened, the color of the skin was slightly yellowish, the dyspnea slight, the mind clear. The patient was a strong young man, well nourished, not fat, non-alcoholic, and remained quietly in bed, and did not offer difficulties to his nurses nor to his physician. I made a very favorable prognosis of a clinical course with crisis upon the seventh or ninth day. In the main, this prognosis was fulfilled, the disease ran a comparatively intense and typical course without interruption and complications, but the crisis only occurred between the eleventh and thirteenth days, and then the malady entered upon the normal epicritical stage. From the typical temperature curve, the entire course of the disease

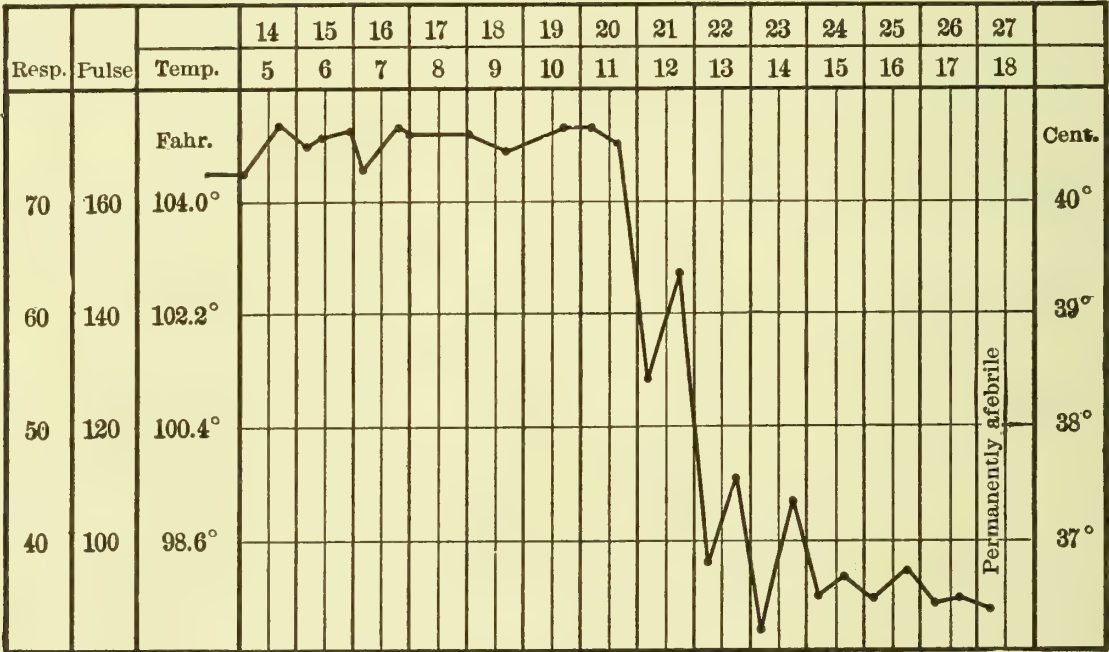


FIG. 37.

can be plainly recognized. The patient was entirely convalescent upon the nineteenth day of the disease, and left the hospital three or four days later. The treatment was simple, as in a regular course no special remedies are necessary.

CASE III (Fig. 38).—C. H., aged twenty-seven, farmer, admitted upon May 3, 1901, discharged June 8th, cured. His pneumonia was quite typical and relatively mild. Upon May 3, 1901, the patient while at his work fell from a ladder, landing upon his back. His comrades lifted him, and, on account of headache and pains in the right side of the chest and the small of the back, after work took him to the hospital. Chill was not present, but vomiting occurred.

The *status præsens* upon May 4th was as follows: Patient a strong young man of good musculature, maintains the active dorsal decubitus. Face markedly red and turgescient, eyes closed (patient cannot be prevailed upon to open them wider than a narrow slit). Large beads of sweat upon the forehead and nose, upon the rest of the body the skin is burning hot, with very little moisture. No herpes of the face; tongue somewhat coated, tremulous on being protruded; both pupils equally wide, reacting promptly to light. Temperature 104.9° F., pulse 124, large, full, good tension; respiration 34, superficial, the left side of the thorax particularly active. Anteriorly below the

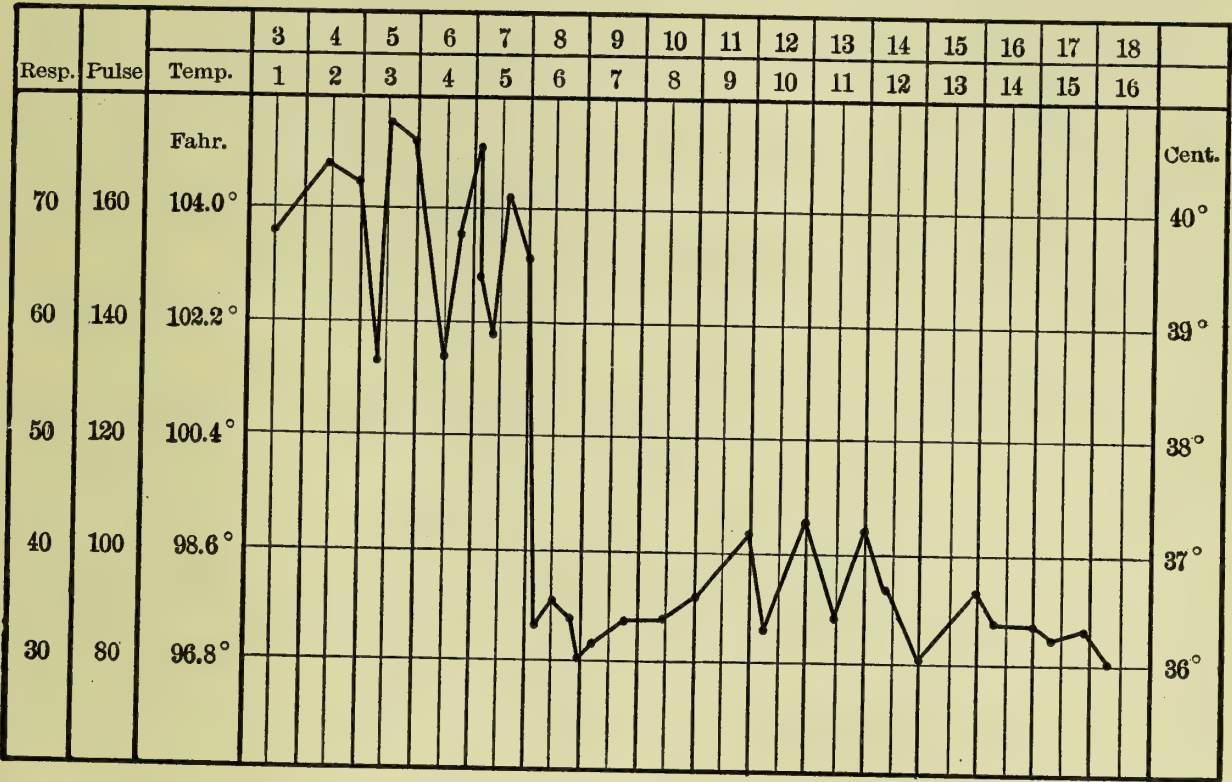


FIG. 38.

clavicle the right side of the thorax is sensitive to pressure. Percussion anteriorly on the right, above, shows distinct dullness up to the upper border of the third rib, in this region the respiratory murmur diminishes, bronchial expiration and a few crackling râles can be heard. Posteriorly upon the right, above, decreased note upon percussion, with tympany, indistinct breathing with prolonged bronchial expiration, and occasional crackling râles.

Over the left lung, distributed piping râles upon breathing, otherwise normal conditions. Brief, painful, paroxysmal cough. The sputum brought up by exertion is tough, sticky (adhering to the sputa cup), glassy, foamy, and of distinct rusty consistence. Nothing abnormal in the heart. The lower border of the liver reaches below the margin of the ribs; the liver is not sensitive to pressure.

The sensorium is somewhat implicated. The patient remembers with difficulty, answers questions slowly, but still correctly.

Urine high-colored, turbid on account of urates, traces of albumin; urobilin. In the sputum numerous diplococci.

Amount of nourishment taken per day: 1 litre of milk, 1 roll, 2 soft-boiled eggs, 1 litre of soup, some wine, mineral water. In the course of the day a solution of codein, 0.1-10, 15 drops three times.

In spite of the relatively intense symptoms, the course of the disease was quite uniform. On the fifth day (see fever curve) crisis occurred, which led to the epicritical stage without marked symptoms of weakness, convalescence finally occurring. Upon the fourteenth day of the disease the dullness cleared, bronchial respiration disappeared and but few crepitant râles remained.

In regard to this very typical case, I must reiterate that the patient, at the onset of the disease, fell from a ladder, and that contusions may be looked upon as a cause

of pneumonia (contusion pneumonia, Litten). However, this can only be explained in the sense that trauma is capable of favoring the development of pneumococci in the lung and thus pneumonia develops in this manner.

Besides these typical, relatively mild cases of pneumonia, I must also refer to other cases which have terminated fatally.

Among these was that of a decrepit old man, sixty-three years of age, who entered the hospital on the seventh day of the disease, in a condition of weakness and high-graded dyspnea; we could not save him in spite of the use of heart tonics and stimulants. He died two days later, upon the ninth day of the disease, with the signs of cardiac asthenia and pulmonary edema. Another patient, aged forty-two, entered the hospital in a serious condition. He showed the physical signs of pneumonia, having been ill 14 days; he was weak, cyanotic, with very rapid pulse, dry cough, no expectoration. We suspected a complication. Repeated exploratory puncture finally showed a purulent exudate in the right thorax (metapneumonic empyema), the pus contained diplococci and streptococci. We referred the patient to the surgical clinic for operation of the empyema (with resection of the ribs).

After having described these cases of pneumonia and emphasized the differences between them, it is my intention to devote the rest of this article to a description of pneumonia in general. I believe this to be necessary, as pneumonia is of special importance and is calculated to interest to a high degree the young as well as the old practitioner. Every physician has an opportunity of seeing many cases of pneumonia, for inflammation of the lungs belongs to the relatively most frequent and most important diseases. It occurs in all classes of society and in every age. Every physician, therefore, must understand this disease and be familiar with its treatment. At the same time this affection belongs to those which were known to physicians of all periods, even to the ancient masters of medicine, we, therefore, find such descriptions in the oldest medical writings and we are able to recognize them readily. This has been the case at all times, the observation of symptoms as well as the description of the treatment has passed through centuries of medical literature, from the foundation of universities and hospitals. Pneumonia forms an integral part of clinical teaching, because it recurs with relative frequency in hospitals and because the affection is suitable for a clinical discourse. It is the *type of an acute febrile disease*, all methods of examination and observation that are required in febrile processes being necessary in this malady, and the disease may also be looked upon as the *type for the treatment of other acute febrile affections*.

In presenting a review of the history of pneumonia, from the time of Hippocrates up to the present period, it will be noted, not without some astonishment, how almost all transformations, improvements, advancements and mistakes which the history of our science shows are reflected in the change which the teachings regarding pneumonia has undergone. Even in antiquity the teachings regarding fever and crisis were essentially associated with pulmonary inflammation, and as regards therapy, the history of venesection is intimately connected with pneumonia. During recent times, pathologic anatomy and scientific clinical investigation, with auscultation, percussion and clinical chemistry, have done their part in this affection, and, finally, the newest branch of pathology, bacteriology, is also the most modern in pneumonia. Still more

characteristic and instructive is the history of the therapy, in which for a long time venesection predominated. With its fall, the therapy of pneumonia lost its certainty, which it only regained in the last decade.

Many physicians (and laymen) have said: What else does the long history of pneumonia teach but error upon error and what is the result: Expectant treatment! In this manner speak those who know no other therapy but a specific one, who wish to be physicians according to diagrammatic representation, not through labor, care and thought. And, as regards the errors, it may be said with equal force: The entire history of the world is nothing but a succession of errors, for every advance is upon the foundation of a former error. Improvement is the enemy of satisfaction! Improvement, i. e., *advance*, relegates the good among the errors, and yet it was the good which was the necessary previous stage to the better! If the history of pneumonia is looked upon in this light, all the advances of our science—pathology and diagnostic methods—will be recognized, and in its failures the advances in therapy will be noted, which to-day stand upon a firm basis without polypragmaty, and by which we may hope to solve the problems along lines that have been begun, those of serum therapy.

The expression *pneumonia* (peripneumonia) is found in the oldest medical manuscripts, and, according to the accurate descriptions of the symptoms of the disease, it cannot be doubted that, in general, i. e., exceptions admitted, the same affection was meant which we to-day designate as pneumonia (inflammation of the lungs). In the works of Hippocrates, the rusty sputum, the fever and the stitch in the side is described, and the celebrated law of crisis of the venerable father of medicine is to-day, for the greatest part, connected with the fever course of pneumonia.

Galen and Aretaeus, the great masters of description of typical pathological pictures, gave an excellent account of the disease.

During the period of scholasticism, the writings regarding this disease accumulated without showing marked advance; the authorities, Hippocrates, Galen and Avicenna, being adhered to.

The anatomical method of investigation brought new advances. Since Morgagni, "the anatomical thought" also developed itself for pneumonia. With Laennec it attained a certain degree of completion.

The older clinicians in Leyden (Boerhaave, van Swieten, as well as the first celebrated Vienna school) still showed many uncertainties and doubtful points. The following description deserves repetition: Boerhaave performed an autopsy upon a youth aged twenty who died of pneumonia on the seventh day. He found the lung markedly distended and very hard, tightly adherent to the diaphragm, bloodless; it sank in water and weighed over 5 pounds. The tissues were filled with a thick, red, fleshy substance.

Maximilian Stoll and Peter Frank disputed much regarding the differentiation between pleurisy and pneumonia.

In an anatomical respect, the investigations of Laennec, 1810 to 1826, were of fundamental importance in pneumonia. He differentiated the well-known stages of pneumonia in a proper manner: (a) engorgement; (b) red hepatization; (c) gray hepatization; (d) resolution. At the same time Laen-

nec described the physical signs which at the bedside make it possible to diagnosticate pneumonia with certainty and permit the recognition of the designated stages of development. The name "hepatization" was given because of the appearance and consistence of the inflamed pulmonary tissue, which is conspicuous on account of its greater compactness and weight.

In the beginning of the nineteenth century the French clinicians Andral, Chomel, Bouillaud followed the teaching of Laennec and completed the symptomatology. In England, particularly Stokes and Walshe were the ones who accepted Laennec's teachings and practiced them.

In Germany, the new teaching found acceptance with difficulty, as may be seen from the description of pneumonia in the 27th volume of the Encyclopedia (Berlin, 1842). Hufeland's writings contain but little of the new thought which arose in France and enlivened the study of medicine. Primarily, the second Vienna School of Physicians which attained just as high a rank as the first, expressed themselves in favor of the plan. Under Rokitansky and Skoda it attained a brilliant development based upon pathological anatomy and upon exact physical diagnosis. Rokitansky, in his text-book on pathological anatomy, gave a more accurate description of pneumonia than has been given by any author up to this time; he designated it *croupous pneumonia*, and Skoda simultaneously developed the semeiology and diagnosis of the disease in a masterful manner. From Vienna the new principles spread over entire Germany. In Berlin the pathological anatomy taught by R. Virchow attained its highest stage, and his teaching also remained authoritative for pneumonia. Virchow gave the disease the name *fibrinous pneumonia*. The teaching under Schönlein, L. Traube, and Wunderlich made great advances. The exact method of auscultation, the manner of examination of the urine, especially the methodical use of the clinical thermometer (first introduced by de Haen in Vienna, developed to a precise clinical method by Wunderlich in Leipsic, v. Baerensprung in Halle, L. Traube in Berlin), markedly promoted the accurate investigation of the course of the disease. The researches of L. Traube regarding crises and critical days developed the following important points regarding fever and the febrile process (Liebermeister, Senator, Leyden,¹ and others), which in the fifth, sixth, and seventh decades of the previous century, occupied German physicians, clinicians, and pathologists.

This is in immediate connection with the newest, the most important *epoch of bacteriology*, which has had such a prominent influence upon our views of infectious morbid processes in general, and not least in extent upon pneumonia.

Pathological Anatomy.—The pathological anatomy of pneumonia even to-day rests upon the basis of the stages described by Laennec. At the height of the disease the infiltrated portion of the lung is tough, compact and airless, so that excised portions sink in water. The color of the hepatized lung is brownish-red, nearly that of the liver. In the first stage of engorgement, the

¹ Untersuchungen über das Fieber. Deutsche Arch. f. klin. Med., 1869, p. 273; 1870, p. 536 u. a. m.

affected pulmonary tissue is not quite airless, it contains fluid, and, upon pressure, exudes a hemorrhagic serous liquid. Upon section the hepatized lung presents a fine granular appearance, in that the small fibrinous plugs which fill the alveoli protrude somewhat in consequence of the inelasticity of the tissue upon the cut surface. Microscopically, the alveoli of the hepatized lung are found filled with a relatively coarse fibrinous plug, and traversed by blood corpuscles and relatively few cells containing nuclei. In the further course of the process numerous leukocytes enter, loosen the fibrin plug and give to the cut surface a grayish-red, granular appearance (reddish-gray hepatization). Finally, the leukocytes predominate (gray hepatization), the coarse infiltrate softens, the fibrin in the alveoli breaks down, is loosened (resolution) and becomes absorbed, and, in this manner, the normal condition of healthy pulmonary tissue is again assumed.

SYMPTOMATOLOGY, DIAGNOSIS

The art of the ancient physicians which enabled them to appreciate the clinical picture ("the physiognomy of the disease") and thus to recognize the disease even to-day awakens our greatest interest. I shall quote the descriptions of the celebrated physicians of ancient times, from which, simultaneously, the advance of medical knowledge may be noted, which at first was quite slow, but later of astonishing rapidity.

Hippocrates has just been mentioned; I shall give the brief, accurate description of Galen and Aurelianus:

Galen says: If, simultaneously, a high fever is added to the great difficulty in respiration, accompanied with anxiety and pain, this disease is called inflammation of the lungs.

Aurelianus writes: The signs of this disease are the following: Hot fever, rapid and severe breathing, short cough, expectoration of the saliva, difficulty in the chest, with or without pain, sensation of threatening asphyxia.

So long as the law of Hippocrates and Galen was accepted, nothing of importance was changed, even the great Hippocratic physicians up to the beginning of the eighteenth century adhering to this teaching: Sydenham, Boerhaave, and the first Vienna physicians (de Haen, van Swieten, Dietl, Peter Frank, Fr. Hoffmann).

According to Boerhaave, who may be mentioned as the greatest authority of that time and whose teaching long remained influential, the "stitch in the side" is the actual principle of the disease, and the differentiation of inflammation of the lung and inflammation of the pleura is very difficult.¹

¹ van Swieten in his celebrated commentary upon Boerhaave's aphorisms writes: "This disease (pleurisy) is present when the patient shows a hot, continuous fever with a hard pulse, severe, sticky, inflammatory pains, which are constantly increased in breathing, in expiration or holding the breath becoming slighter, and accompanied with continued cough, which produces pain, and, for this reason, causes choking, a cough which commonly goes hand in hand with a bloody expectoration, rarely existing without it. In this manner Aretaeus and Alexander Trallianus described the disease, and physicians are not yet unanimous regarding the region in which this inflammation is found. Aretaeus says: 'Under the ribs and over the inner part of the chest there is a strong skin. If a phlegmon is present in this and fever and expectoration occur,

Among the Vienna clinicians, Maximilian Stoll must be mentioned, who says of true pulmonary inflammation (page 32): The signs of this malady are, 1. The general signs of inflammatory fever; 2. The especial signs of the inflamed lung, continued pressure upon the chest, with dry or moist, bloody cough, by which deep breathing is made particularly difficult. If the disease affects both lungs simultaneously to a marked extent, unavoidable, rapid death follows.

Hufeland writes (*Encheiridion med.*, 1837, p. 180) in regard to the diagnosis of pneumonitis, pneumonia, inflammation of the lung: Its symptoms are a stitch or pain, so that the patient cannot breathe properly; hard, full pulse; cough; expectoration, serous or gelatinous, mucus, then bloody, purulent-inflammatory; red urine. Recently, there are also signs by hearing (stethoscopy and percussion); these have been advised in the diagnosis of diseases of the chest, but these signs are deceptive and by them alone the presence of an inflammation will never be recognized. Duration of the disease: seven to fourteen to twenty-one days.

Crisis.—*Termination* in resolution or suppuration or hardening (tubercles).

From these brief sketches regarding the diagnosis of pneumonia, which existed in various epochs of medicine, the masterly skill of the ancient physician is recognized in the observation of the sick; the fully developed clinical picture of pneumonia was drawn in brief, sharp characters and judged correctly. But the certainty of diagnosis, the thoroughness, and the exact knowledge of individualities which are in our possession to-day were entirely wanting; the knowledge of the onset of the disease and its further course was very deficient; the characteristic febrile course, as well as the course of the local processes, was particularly unknown. Here only thermometric and physical investigation, the great acquisitions of the past century, could bring advance.

The first appearance and development of a disease is frequently so characteristic that it is of great importance in diagnosis. This is especially the case in pneumonia. This disease begins—usually without noteworthy prodromal phenomena—in the majority of cases, with a well developed *chill*; the patient shakes from cold, the face is hollow, bluish, as are also the hands, especially the finger-nails. After from one to two hours the chill ceases, giving place to fever-heat which, if measured with the thermometer, shows an increased rise of temperature to about 104° F. The face is now turgescient, markedly reddened (fever redness, fever turgescence), the skin is hot, dry or somewhat moist. The fever continues, accompanied by an increased pulse-frequency. The respiration is increased, often sighing. *Cough, stitch in the side* and *expectoration* occur, the latter, occasionally, from the start, being *rusty, tough, foamy*.

After having obtained the history of the patient regarding the onset and

the illness is called "the stitch in the side." As, however, stitch in the side and inflammation of the lung are two ills which are closely related, often arising from the same cause, the most celebrated men in medicine have been of the opinion that in both diseases the same region is affected, namely the lung.' The celebrated Fr. Hoffmann advised calling the disease pleuropneumonia or peripneumo-pleuritis.

previous course of the disease, we determine his *status præsens*. This includes, firstly, *the general symptoms*, which may be noted from careful observation of the patient, and *secondly, the local symptoms*, which, as a rule, can only be ascertained and investigated by special *methods of examination*. Such methods are: the thermometric and physical investigation, microscopical examination of the sputum, the chemico-microscopical analysis of the urine, eventually also of the blood.

Only from the result of such a complete methodical investigation can the *diagnosis of the disease* be made; it is not sufficient to give the affection a name, but the diagnosis includes the appreciation of special conditions of the individual case, especially the day of the onset, the seat and distribution of the process, the intensity of the general symptoms (toxic action). Only thus, from the diagnosis, can the knowledge of the danger (prognosis), and the ways and means which are to bring the disease to a favorable termination (therapy), be determined. To the first thorough examination, the continued daily observation of the patient must be added, by which the daily changes and the advance of the disease may be recognized.

The special examination of the patient begins with the investigation of the *febrile phenomena* and the *course of the fever*. Regular temperature records (taken in the axilla) one, two to three times daily, in the morning between eight and nine o'clock, in the afternoon between twelve and one, and in the evening between five and six; is at present a necessary desideratum, the drawing of the fever curve ("*umbra morbi*") allows us to recognize the typical course of the fever.

1. **The fever.** In the majority of cases, the disease begins abruptly or at least more or less suddenly. As a rule, the onset of the disease is characterized by a *chill*, which is not infrequently associated with vomiting or introduced by it; in children it happens, as in other febrile diseases, that the affection is introduced by *convulsions*. The patient takes to bed, wraps himself in his coverings, but is, nevertheless, shaken by the chill. Above I have described the appearance of a patient in this stage. After the chill has passed the patient feels somewhat better but is decidedly ill. He now has fever, 104° F. (more or less), the pulse amounts to 100 to 120 beats and usually a short, at first only dry, cough occurs, and with this there is pain in one or the other side of the chest (stitch in the side).

The patient, as a rule, *remains in bed*. On the second day the clinical picture is about the same. The face is red and turgescient, usually showing a yellowish tinge, the temperature between 102.2° F. and 104° F., short, painful cough; the expectoration is now usually *pneumonic*, the respiration is increased; the patient complains a great deal.

Upon the third day there is frequently a decline in the fever without decided amelioration of the other symptoms, without improvement of the general symptoms, with continuance of the pain and with pneumonic expectoration.

Upon the fourth day the disease reaches its acme, fever and pulse frequency are high, the former 104° F. and more, pulse 100 to 120. Respiratory frequency 30-40-60 and more; the patient moans, complains much, he can move about but little, frequently delirium occurs.

Not rarely, from the fifth to the sixth day, an amelioration occurs, which is usually of *favorable prognosis*, but which is not rarely followed by a second exacerbation with fulminant symptoms (*perturbatio critica*). The fever again rises to 104° F. to 105.8° F., all symptoms increase so that the condition becomes serious. With anxiety, the physician looks toward the appearance of the expected crisis upon the seventh day.

With the seventh or eighth day the symptoms decline, the patient becomes more quiet, respiration is better, sweating occurs, and the temperature falls continuously for one to two days, until normal or subnormal ranges are reached.

The rapid decline in fever is designated crisis; we speak of *rapid crisis* if the temperature falls within twelve to twenty-four hours, of a *protracted crisis* when the decline shows slight interruption, lasting from two to three days, and *interrupted crisis* (discontinued) if a new and relatively brief exacerbation occurs before defervescence takes place; a *pseudocrisis* is a fall in temperature to nearly normal, without definite defervescence, followed by a fresh exacerbation of the disease: "The crises of pneumonia upon the third day are mostly deceptive," says L. Traube. The physician should not rejoice too early.

Critical collapse is to be feared if with a fall in temperature the already weakened powers of the patient decline still more, the pulse becomes weaker and more frequent, profuse sweating occurs, the temperature falling far below normal, to 96.8° F. or 95° F. or even lower. With increasing weakness, cyanosis occurs, fluttering pulse, râles, foamy expectoration (pulmonary edema), and with the signs of cardiac and pulmonary paralysis, death may occur.

To prevent this *epicritical collapse* in time, and to treat it correctly and carefully upon its first appearance, is one of the most important duties of the physician.

With *completed crisis* the affection, as a rule, has terminated, the danger is over, convalescence occurring more or less rapidly. The physician, however, must not forget that in the *epicritical stage* considerable danger still threatens and a number of sequels may occur, which may result in prolonged invalidism, even giving rise to a fatal termination. In the majority of cases, naturally, with the completed crisis, the danger is as good as over and the expression "The patient is through" is justified.

The signs of a favorable crisis are: If with a fall in temperature a corresponding drop in pulse frequency occurs, if the pulse is good, relatively slow and strong, the respiration relatively quiet, and the subjective condition of the patient decidedly better, when slight perspiration (resembling dew) occurs, sleep and quiet appear.

The crisis occurs most frequently between the sixth and ninth days, not rarely even upon the fifth or as late as the tenth or eleventh days, or it may be longer than this, not taking place until the fourteenth day or later. In elderly patients we are not even then certain that relapses will not occur; in them cases are observed in which the relapses, insignificant in themselves, recur and recur, and ultimately exhaust the strength of the patient. Newly appearing and continued fever at the crisis points to complications and sequels (empyema, pulmonary abscess, gangrene, etc.).

In rare cases, upon the first or even upon the second day, a *definite* crisis has been observed in pneumonia (one to two day pneumonia), which then shows very mild symptoms: chill, fever, and crepitant râles at circumscribed areas in the lungs. In such cases it was formerly believed that the development of pneumonia was "aborted" by venesection; to-day, however, we must ascribe it to the peculiar mild form of the affection and cannot admit that therapy has any marked part in this if the pneumonia runs so mild a course and in so short a time.

Pneumonia runs its course *locally* with relapses, this is also true of the fever. Demonstrable recrudescences are characterized by protracted fever; well developed varieties of this kind which last fourteen days or more and invade other parts of the lungs are designated as *wandering pneumonia* (pneumonia migrans).

The most important *febrile symptoms* are (besides the rise in temperature) the changes in the pulse, the respiration, the urine and the symptoms on the part of the nervous system.

The **pulse** in pneumonia is strong, full, high (pulsus celer), the arteries are well and widely expanded (pulsus magnus), rarely dicrotic. The pulse frequency is at least 80 to 100 or even more than this; a pulse frequency of 120 or more in adults shows a serious prognosis. Children and females bear a high pulse frequency comparatively well, the aged for the most part badly. From the fifth day up to the time of crisis the pulse frequency usually rises. The frequency of the pulse and its tension (power) are of importance in prognosis. If both correspond with the fall in the temperature this is a good sign. Rapid rise of the pulse frequency with diminution in arterial tension indicates collapse.

After the completed crisis the *pulse* returns to normal, however, *not always immediately*. Occasionally for a longer period it remains abnormally frequent. Sometimes, even in youthful patients and after a good, rapid crisis, it becomes abnormally slow, 40 to 44 per minute. Occasionally it may *intermit* simultaneously; both these conditions are to be regarded as signs of cardiac weakness but with proper care the condition is without danger.

The **respiration** is in the main, but by no means always, parallel with both the fever and the pulse frequency. At the acme of the disease it is rapid, the assistance of all the auxiliary muscles are called into action, and only from 40 to 60 per minute, superficial, and of slight expansion on account of the pain. Deeper inspirations are prevented by the pain. With a respiratory frequency as great as this, the patient can only speak with difficulty, is scarcely able to swallow, but he does not by any means always have a sensation of air hunger. Marked dyspnea, complaints of shortness of breath are eventually of evil prognosis particularly if distinct cyanosis occurs and the pulse becomes weak.

The *urine* and the symptoms on the part of the *nervous system* will be described later on.

2. Examination of the Local Process.—It requires no explanation in stating how important the physical examination is, not only regarding the diagnosis but also in the recognition of the course and the complications. The

intensity of the inflammation does not actually run parallel to the development of the local processes, but in the main it is for a great part dependent upon it. Extensive pneumonias are usually accompanied with severe symptoms, bilateral pneumonias in Schönlein's time were regarded as almost absolutely fatal. Percussion is of the greatest importance in the recognition of wandering pneumonia.

Palpation of the thorax is not of like importance, and testing the pleural pain by pressure with the finger is obsolete.

Percussion with the back of the patient somewhat elevated, first carried out in the anterior parts of the chest determines whether the seat of the pneumonic process is present there; it is to be especially investigated whether an upper-lobe pneumonia is present, which shows itself by a more or less distinct dulness above and below the clavicle. At the onset of engorgement (first stage) dulness is not rarely absent and the percussion note is somewhat higher than upon the other side, or perhaps, inversely, deeper and slightly tympanic. The onset of pneumonic infiltration is determined better by auscultation than by percussion. In the further course of the affection, after complete hepatization has occurred, the percussion note is dull, but with this it is slightly tympanic; in complete hepatization there is complete dulness as in percussing the liver.

Now, after having the patient sit up, the posterior side of the thorax is percussed in the same manner. We percuss first along the vertebral column (the patient sits somewhat bent forward, the arms hanging flaccidly or stretched somewhat forward). In this percussion along the vertebral column, dulness of the apices or in the lower parts of the lungs is to be observed (from the angle of the scapula downward). The shoulder blade is then percussed as well as the lateral aspect of the chest, not only the lower parts of the thorax but eventually also the axillary region. In the frequent cases of lower-lobe pneumonia, it is not rarely determined that the dull percussion note in the region of dulness from above downward diminishes in intensity, a condition to which formerly more attention was attached than now; from this it may be concluded that the dulness is not due to fluid (pleuritic exudate), which gives an increasing dulness from above downward. Earlier physical diagnosis, as has been mentioned above, has busied itself much in differentiation between pneumonia and pleurisy by physical examination. Such differential diagnosis is at present of slight value, as in doubtful cases aspiration by means of a Pravaz syringe will readily decide the case.

The extent of the pneumonia as ascertained by percussion and auscultation is important in estimating the disease.

In an earlier period (Skoda, Traube), importance was attached to determining by palpation whether we were dealing with lobar pneumonia (in contrast to lobular pneumonia), therefore, whether the hepatization included a particular lobe of the lung. As a rule, the lower lobe is the seat of hepatization, posteriorly it reaches in the thorax from the height of the spine of the scapula downward. The upper lobe, on the other hand, posteriorly takes in the area from apex of the thorax up to the spine of the scapula and anteriorly reaches to the fourth rib.

The middle lobe (as is well known, only present upon the right side)

takes in the greatest part of the lateral wall and a part of the anterior wall from the fifth to the seventh rib.

No very great value is at present attached to determining these boundaries as it is well known that pneumonia does not strictly limit itself to the boundaries of a pulmonary lobe.

With the fall of the fever (crisis) the disease, as a rule, has reached its end, the dulness (hepatization) clears (in the period of resolution), and disappears completely, particularly in youthful individuals, occasionally very rapidly within a few days. In other cases resolution lasts many weeks (*delayed resolution*). Rarely after the crisis dulness increases in the circumscribed area, which signifies that hepatization is not yet quite complete or has only reached its complete limitation after the crisis.

Auscultation at the acme of hepatization reveals loud, blowing, *bronchial respiration*, in very compact hepatization almost amphoric respiration; the râles (small or crackling) are absent at this time or are very sparse. Bronchial breathing is loudest over the large bronchus, posteriorly near the vertebral column. Not infrequently it is heard upon the healthy side if hepatization is very compact, without the lung being affected in this area. The second, still more important auscultatory sign is *crepitation*, crepitant râles (similar to the sound made by combing the hair or rubbing the hair together with the fingers); it arises in the alveoli which are filled with a fluid exudate (in the stage of engorgement and during the time of resolution), if upon deep inspiration air is still capable of entering, for this reason it is almost exclusively inspiratory. (Expiratory small moist râles [subcrepitant râles], resembling crepitant râles may arise in the small bronchioles.) This phenomenon always indicates an affection of the alveoli, and, in combination with the other characteristic symptoms, denotes the presence, the location and the extent of a pneumonic infiltration. The crepitant râles are most profuse in the stage of resolution, although, it must be remembered that resolution often begins in one area while other portions of the lobe are still implicated in an advancing hepatization.

Clearing of dulness and the appearance of crepitant râles, which is gradually accompanied with vesicular respiration, indicate convalescence, denoting absorption of the pneumonic local affection. The further the clearing and resorption advance the larger the râles become; finally, after complete resolution there is again pure vesicular respiration without râles.

The other auscultatory phenomena, small râles, indistinct respiration, bronchophony and ægophony, as well as testing the vocal fremitus, which was formerly much described, are of slighter importance than was then attached to them, and this condition may be omitted here. The friction sound also has no decided importance. Nevertheless, I should not fail to remark that a deviation from the usual typical course in the physical phenomena of resolution indicates complications or sequels.

In conclusion I should like to discuss the question, how often the careful physician is to examine a patient with pneumonia. It is self-evident that he is to inquire daily (two or three times) regarding the condition of his patient, and that he must observe the course of the affection and the fever; but it is not absolutely necessary to make a physical examination every day

or even every other day, provided there are no distinct indications which appear to be so important as to require an especially frequent examination. *To-day we are no longer of the opinion, as we were forty years ago, that a conscientious physician should examine as much as possible.* The course of the disease may be observed from the symptoms as soon as the diagnosis "pneumonia" is decided. We must much more constantly ask ourselves whether the examination is necessary or desirable in the interest of the patient, or whether for his good it had better be omitted. Seriously ill pneumonics, with difficult respiration and weakness, are more harmed by sitting up and examination than is compensated for by the process. This is especially the case in severe affections, frequently at the time of crisis; the patient, therefore, had better be let alone. However, if it be necessary to examine him, care should be taken that he is properly assisted in sitting so that he need not use any muscular power and that his respiration does not become more difficult.

In the first days of the disease usually the sitting up and the examination will not hurt him, the exercise is rather beneficial to him.

Following the physical examination of the lungs, that of the heart, the liver, spleen, intestines, bladder, etc., is to be undertaken, but I have nothing particular to remark in this connection.

3. The examination of the **expectoration** is of importance.

The *rusty-colored, rubiginous sputum* is the characteristic expectoration of pneumonia. It is pathognomonic in so far as it does not occur in any other disease in so marked a form, and that it occurs in pneumonia in the greatest majority of cases. Only rarely in disease of the heart and pulmonary edema will a similar sputum be expectorated; on the other hand, the pneumonic sputum is not always distinctly rusty. By the ancient authors it is only designated as bloody. Besides the exquisitely rubiginous sputum a hemorrhagic sputum is also noted (rusty-black, blackish) or a pale, rust color, or a grass-green or citron-yellow sputum. Occasionally pneumonic sputum shows no bloody discoloration, apart from the characteristic color of the sputum of patients with engorgement and beginning hepatization, tough, sticky, foamy and transparent, i. e., admixed with profuse cells, adhering to the side of the cup, or slowly flowing downward; further on, it becomes less tough and glassy, somewhat more turbid (with the addition of cellular elements). With completed hepatization, when the transition into resolution occurs, the sputum changes to a pale rusty, citron-yellow, and finally loses this color, becoming gray, or greenish-gray, very turbid and opaque. Not infrequently, however, with the relapse of pneumonia, the rubiginous sputum reappears, which again decolorizes after two or three days. If the sputum is carefully examined at the height of hepatization or at the beginning of resolution, smaller or larger flocculi are found, which microscopically may be recognized as fibrin, which, with advancing resolution, becomes softer and richer in cells and then finally disappears. These small, fine fibrin flocculi at the onset of the disease are not unimportant for the diagnosis. Not rarely also larger and longer fibrin threads covered with blood are coughed up, occasionally even large branching fibrin coagula.

Grass-green sputum occasionally occurs in pneumonia, without a special reason, or in a complication with jaundice, or it indicates the formation of a

pulmonary abscess or of a caseous pneumonia. For this reason the presence of grass-green sputum requires attention.

Finally, we must discuss the *bacteriological examination* of the sputum in pneumonia (staining). Primarily we are concerned with the determination of the characteristic pneumococci, which in themselves are no proof as the same diplococci also occur in the saliva in normal persons. Further, the presence of streptococci and tubercle bacilli is to be noted. If important questions are concerned which are to be decided by the bacteriological examination it is not uncommonly necessary to make cultures or to carry out animal experiments (rabbits, mice). We shall recur to these points.

The sputum of the pneumonic is collected in a glass without water and is poured upon a flat white plate for examination. In this manner the small fibrin flocculi as well as the grayish white mucus flakes may be taken out for microscopical and bacteriological examination.

4. **The urine** in pneumonia requires especial consideration; it has the marked properties of febrile urine, it is red ("high-colored"), specific gravity 1015 to 1025 to 1030, scant, acid in reaction, contains a trace of albumin (*febrile albuminuria*), and frequently also a trace of biliary coloring matter or urobilin. At the time of the crisis a large sediment of uric acid or urate salts are precipitated (*urina critica*, *sedimentum lateritium*). Even a day previously, while the urine is still dark and clear, a similar profuse precipitate may be obtained (upon cooling or by the addition of a drop of acetic acid) which Schönlein looked upon as a latent crisis, precursor of the actual crisis, and therefore a good sign.

In the year 1850, Redtenbacher in Vienna (*Zeitschr. d. Wiener Aerzte*, vi, 373) made the surprising discovery that the urine of pneumonics at the height of the disease does not contain chlorids. He explained this change in the presence of the chlorids in the massive exudate in the lungs and in the profuse leukocyte production. L. Traube was inclined to look upon the cause as the withdrawal of nourishment during fever, and was able, by a copious administration of nourishment during fever, and was able, by a back into the urine again. But this was not a proof against Redtenbacher's views.

Professor Röhmann (Breslau) found, by careful weighing, that the chlorids are completely absorbed from the intestine, that, therefore, a retention occurs in the body as a result of metabolism in fever.

Huchard proposed to supply the absent chlorids by injection of salt water (it has, however, not been proven that the object is attained in this manner).

Slight (febrile) albuminuria is not constant, but is frequently without importance for prognosis.

More marked albuminuria is observed: 1, in patients who have formerly recovered from nephritis (from which recovery usually occurs); 2, in chronic nephritis, particularly in advanced age.

Usually the albumin in the urine disappears with the crisis. Rarely does an actual acute nephritis occur as a sequel. This also usually terminates favorably, but it always requires careful treatment and is not without danger.

The existence of a chronic nephritis in older persons with arteriosclerosis

must be considered. This is not infrequently discovered during a pneumonia, and such cases show a questionable and even serious prognosis.

Peptonuria (*albumosuria*) is frequently met with after the crisis. It is in connection with resolution, the liquefaction of the pneumonic exudate, which, according to the latest investigations of Fr. Müller, corresponds to a digestive process, with a profuse formation of albumoses (deutero-albumose).

The diazo-reaction at the height of the disease is quite frequent (Ehrlich, Michaelis), but of no importance in a prognostic respect.

5. **The blood** of pneumonics has been the subject of attention from an early date. The frequency of venesection gave an opportunity and a cause to observe a conspicuously large formation of the so-called blood-cake upon coagulation. This was regarded as a sign of inflammation, and in particular of inflammation of the blood (hemitis, crusta inflammatoria, buffy coat).

Andral and Gavaret, in their celebrated experiments, determined the unusual increase of fibrin in all pneumonias and pleurisies combined with fever. This fact was confirmed by Th. Simon (Berlin, *Handbuch der angewandten Chemie*, 1841); on the other hand, Simon found the amount of hemoglobin *below* that of normal blood. The latter will correspond with the recent investigations of Bollinger (Munich), who called attention to the conspicuous pallor and anemia of the cadaver in pneumonia. According to Zimmermann's investigations, at the onset of pneumonia the fibrin filaments are rather diminished, increasing, however, upon the first day, which continues with the further development of the local process. He found the fibrin filaments in the blood of pneumonia rarely below $\frac{1}{2}$ per cent. or 1 per cent., the crusta phlogistica of unusual size and firmness; in the cadaver, also profuse fibrin coagula in the heart and in the vessels.

Later hematological investigations in pneumonia have been made by Prochaska, Becker, P. Jacob, H. Mackenzie; particularly in regard to the white blood cells (leukocytosis) and the occurrence of pneumococci in the blood.

Prochaska, by means of a syringe, withdrew the blood of pneumonics from a vein of the arm and cultivated it upon agar; in ten cases he demonstrated *pneumococci*. Other authors found pneumococci but rarely, particularly in severe cases, in the blood; the presence of cocci in the blood was mostly looked upon as an unfavorable prognostic sign. Lately Eichhorst in 50 cases of pneumonia found cocci in the blood forty times; he attaches no particular prognostic importance to this finding. A. Fränkel has confirmed Eichhorst's reports; he even goes further and remarks that pneumococci are found in all cases in the blood in pneumonia, and not only at the height of the disease but even after termination of the affection, as has already been shown by Prochaska who was able to determine them upon the second and third days after the crisis. To determine pneumococci in the blood, according to Fränkel, a larger quantity of blood must be taken for culture and must be placed upon a fluid culture media (bouillon), which is particularly suited for the growth of the pneumococci.

Hector Mackenzie (*Diseases of the Respiratory System*, St. Thomas's Hospital) states the following regarding the blood changes in pneumonia: Leukocytosis (according to Stengel, effect of the toxins) is observed in croupous and

catarrhal pneumonia. The eosinophile cells are decreased: Leukocytosis, as a rule, is a favorable sign. Inversely, the absence of leukocytosis (particularly in children) is not necessarily to be considered an unfavorable sign. Continuance of the leukocytosis after the crisis points to complications.

E. Becker (Hematological investigations. *Deutsche med. Wochenschr.*, 1900, aus der Klinik von Gerhardt) found:

1. High-graded leukocytosis (in more than 20 per cent. of the investigated cases) always indicates severe infection with a good reaction;

2. Medium leukocytosis (12 per cent. to 16 per cent.) may be due to slight infection with sufficient reaction;

3. Slight or absent leukocytosis may be due to slight or mild infection, however, it depends for the most part upon insufficient reaction of the individual and, therefore, makes the prognosis unfavorable;

4. Eosinophile cells only appear after the crisis;

5. The red blood cells show a slight decrease, their number diminishing to about 3,500,000; few nucleated blood corpuscles. The prognosis in post-febrile anemia, upon the whole, is unfavorable. In a severe case in which, however, recovery occurred, Becker recognized myelocytes up to 0.09 per cent. during the last days of fever.

Paesler (Leipsic) (*Zur Behandlung der fibrinösen Pneumonie. Münchener med. Wochenschr.*, 1900) explains leukocytosis, according to the theory of Buchner and those of his followers, in the manner that the increase of the leukocytes in pneumonia protects the organism against the invasion of bacteria, the absence of which may be decisive for an unfavorable course of the disease.

In connection with this, in the treatment of pulmonary inflammation, v. Jaksch proposed to employ such remedies as increase leukocytosis.

P. Jacob (*Bacteriological Investigations in Pneumonia*, 1900) determined that in the usual cases of pneumonia, up to the crisis and for a short time after the crisis, decided polynuclear hyperleukocytosis is present, which for the most part declines to the normal shortly after the crisis. During the pseudocrisis, however, a diminution of the hyperleukocytosis can usually not be noted. A direct parallel condition between the height of the hyperleukocytosis and the size of the area implicated by pneumonia cannot be determined. Nevertheless, it may be regarded as a constant rule that those cases of pneumonia in which no increase of the white blood corpuscles can be recognized at the onset of the disease present an unfavorable prognosis. The reason for the absence of hyperleukocytosis in these cases must be due to the circumstance that in these cases probably extraordinarily powerful toxins are present which force the emigrated leukocytes coming from the hematopoietic organs to enter the capillaries of the internal organs, that is to prevent an increase of leukocytes in the peripheral blood. This theory is based particularly upon the experimental labors which were carried on about 1890, in the first Medical University Clinic, by Goldscheider and Jacob. They came to the following conclusion:

Hyperleukocytosis depends upon a process in which the leukocytes—and, as it appears, particularly the polynuclear—are forced into the capillaries and smaller vessels of particular organs and are retained there; a destruction

of white blood corpuscles in this phenomenon, if at all present, plays but a very subordinate rôle.

Hyperleukocytosis is due to the fact that the material which enters the lymph tracts causes an increased transportation of white blood corpuscles into the circulation. In this process, probably only to a slight degree is there a new formation of leukocyte elements; hyperleukocytosis appears to result particularly in that from the hematopoietic organs, particularly the bone marrow, numerous elements among these, also the frequent polynuclear ones, which are present there and prepared to be sent into the circulation as the result of the attack, are forced into the blood stream.

If an infectious disease attacks the organism it depends upon the amount of toxins excreted by the bacteria in how far the activity of the leukocytes will be enfolded. If this amount is a very great one, as a rule hyperleukocytosis does not occur, as the negative chemotactic influence of this toxin upon the white corpuscles is too great to cause a marked dissemination of them from the hematopoietic organs. If the amount of toxin, however, is but a medium or small one, after a shorter or longer period hyperleukocytosis occurs; the leukocytes which freshly enter the blood stream excrete their bactericidal products which take up the toxins excreted by the bacteria and, according to the proportional amounts, terminate the condition favorably or unfavorably.

I favor the view that the increase of the fibrin and leukocytes in the blood represents an analogy to the local process in which a moderate accumulation of fibrin and further on of leukocytes occurs. Both these conditions might be referred to a peculiarity of the pneumococci. The blood takes part in the local process, even though to a slight degree; it contains pneumococci, produces increased fibrin and leukocytes. My opinion is, that the process of development of the toxins occurs *locally in the pneumonic hepatization* and that here also, locally, the pneumococci are rendered inactive and are destroyed. In this the leukocytes which, in connection with Ehrlich's theories, we may look upon as the carriers of the immune products, play the main rôle. According to the investigations of M. Wassermann, from the first Medical Clinic, in 1899, the immune products of pneumonia are formed in the bone marrow and from here are carried to the hepatized lung by means of the leukocytes. However, the entire process, the accumulation of leukocytes, their destruction, the liberation of immune products, immunization itself, is in the main a process limited to the pneumonic infiltrate.

6. Nervous System.—In typical pneumonia the mind for the most part is clear, but not rarely in the asthenic form, particularly in an early stage, mild delirium occurs, which increases after the crisis and occasionally even becomes markedly furibund, and may be associated with delirium tremens. Of this delirium, its character, prognosis and treatment we have already spoken (see page 534).

Delirium is usually preceded by *insomnia*, the treatment of which requires full consideration. Not only is the patient exhausted by this loss of sleep, but the unrest (*agitatio*) is increased; to this is added that in continued wakefulness, thoughts and cares occupy the mind of the patient which diminish his psychic power. Formerly, physicians feared the use of narcotics; these

remedies weakened the heart and in this way brought danger; this is, however, only true of large doses which were formerly employed, in which sleep was *forced*: 1 grain of morphia (0.06) per day or 3 to 4 grams of chloral. These produced sleep, but the sleep readily terminated in coma and destruction. Now we early employ small doses of morphia subcutaneously or in a suppository (0.005 to 0.01), these should be used during the day at a time during the remission of the fever; if these are well borne and produce sleep they are to be repeated toward evening, eventually even in the morning. Larger doses are necessary if delirium is present. After the crisis, frequently unrest and insomnia occur, but even sleep lasting an hour has a salutary effect. This treatment, however, must always be guardedly employed. I shall never forget the case of a man aged forty who was attacked by severe pneumonia and who was himself very anxious regarding his condition; the symptoms in general were not so severe, but a certain sensation of weakness was obvious. *After the crisis* he could not sleep and began to have delirium, he was given a small injection of morphia, 0.005; as he did not sleep, the dose was repeated, sleep appeared to occur, but simultaneously he ceased to breathe; I was called at once, found the patient almost without respiration and without pulse. By friction and by artificial respiration, as well as a clyster of a bottle of red wine, he returned to consciousness. Toward morning quiet sleep occurred and convalescence began.

A case of this kind shows how difficult the position of the physician may be, but in spite of this we cannot dispense with narcotics. Their use is most dangerous in cyanosis or coma with severe agitation and delirium, but even here, occasionally, they must be employed to save life.

DURATION, COURSE, AND TERMINATION OF PNEUMONIA

The duration of pneumonia may be from one day to three weeks, the cases lasting but a few days (Thomas: three cases of two-day pneumonia; Leube: one case of pneumonia lasting one day, and others) were previously described by Wunderlich as *abortive forms* of pneumonia; Finkler designates them as *rudimentary forms*.¹

A typical variety of the disease which lasts from one to two weeks allows the recognition of the following **stages** in a normal course:

1. *A stage of incubation and prodromal stage* is but rarely developed. Occasionally, prior to the outbreak of the affection, for a long time cough and malaise may precede, particularly at a season in which influenza prevails. Schönlein supposed that pneumonia usually developed from a bronchial catarrh. The possibility of such connection is not to be denied, as the diplococcus pneumonia is always present in the mouth and may descend through the bronchi into the pulmonary alveoli; if it there meets with a prepared soil, the conditions for the development of the pneumonia are present. As a matter of fact the process is not so simple. I mentioned this to emphasize that particularly during the time of influenza, serious bronchial catarrhs are to be carefully treated.

¹ There are also (mild) pneumonias in elderly persons, with very characteristic physical signs, and rusty sputum, which run an afebrile course.

2. *The initial stage* is almost constantly characterized by a chill (with vomiting). From this there develops the third stage.

3. *The stage of development* in which the affection reaches its height (fever, dulness, crepitant râles, bronchial breathing, rusty sputum).

4. *Stage of acme.* The height of the disease is usually reached upon the fifth day, but the affection may continue to increase up to the seventh day and even longer and suddenly take a change for the better with the crisis. This period in all severe cases is one of great anxiety for the physician and the relatives of the patient. Anxiously a cessation is looked for—almost from hour to hour—without being able to forcibly bring it about; under the most threatening symptoms the affection drags along for two, three or four days. The physician must show the greatest circumspection and firmness to control and hold the situation in the presence of the family.

5. *Stage of crisis.* A stage of decline is usually absent, but not always. The longed-for cessation upon the fifth to the seventh day brings an amelioration of the distressing symptoms and a lessening of the imminent danger to life. Not rarely one or more exacerbations follow until complete defervescence occurs, upon the seventh, ninth, eleventh, or even upon the fourteenth day. The pneumonic process may even be protracted longer than this (in old persons, complications) and thus by its duration give rise to anxiety and danger.

Defervescence occurs by crisis or lysis. A protracted crisis is more desirable. A sudden crisis is not infrequently combined with collapse (temperature 96.8° to 95° F., loss of strength, threatening pulmonary edema). Here the greatest care is necessary.

6. *The epicritical stage.* It is usually supposed that with the crisis the danger is over, the patient has recovered. In youthful and in strong individuals in the typical course of pneumonia this is quite true, but this is not universally so. In severe cases after the crisis the patient is weakened to a high degree, pale, emaciated; his pulse is small, appetite is missing, the administration of nourishment is attended with difficulty. Disturbing cough, insomnia, unrest continue. With this, there is danger of cardiac paralysis (heart failure) or pulmonary embolism. The patient dare not sit up, must be nursed with the greatest care; here after two or three days strength begins to return.¹

7. *Stage of convalescence.* If after the crisis the strength is good, and sleep and appetite are present, the labor of the physician is easy. On the other hand, if these conditions are not present it may be very difficult. The possibility of sequels or serious intercurrent conditions must be thought of.

I should like to compare the task of the physician in convalescence to the position of a general who has won a battle. Both must understand how to utilize the victory in order not to lose what has been won.

In the stage of convalescence the pneumonic infiltration resolves (reso-

¹ By some authors the epicritical stage is not recognized. I hold that convalescence cannot be reckoned from the moment of defervescence, but only when distinct signs of an amelioration of the general conditions are present. In justification of this view, I may refer to the conditions of metabolism immediately after defervescence. I shall consider them later on.

lution). The advance of resolution is to be followed by great precision in auscultation and percussion. However, the physician is not to examine too often. ("The patient is examined much too frequently," said Frerichs.) The examination is to be in the interest of the patient (compare page 547). With complete resolution, an increase in strength and the return of appetite, convalescence is ended in so far that the patient may leave his bed.

8. *Period of getting out of bed.* This also requires care. After a severe disease I first allow the patient to be placed in another bed or laid upon a lounge or to sit in a chair. He may remain up from one to two hours (in his room) and must be observed. If he becomes pale tired, and the pulse becomes small, he must be brought back to bed sooner. Upon the second day he again arises for two hours and only now do I make the trial, with assistance, of allowing him to stand upon his feet and of walking a few steps. We are upon the right road if upon the morning after getting up for the first time the patient feels better, i. e., sleep, appetite, and mental condition are satisfactory. Unrest and impatience, on the other hand, are not good. Sleep may be assisted by small doses of morphia. As a standing rule, the physician may regard the period in which the patient leaves his bed after a severe illness as a very important one, which must be conducted gradually and with care, and that time which here appears to be superfluous is compensated for later on by a more rapid recovery.

The most frequent **terminations** of pneumonia are:

1. *Complete resolution after the crisis (crisis bona)* and
2. *Exitus letalis (crisis mala).*

Besides these two, which we have already discussed, other rarer forms of termination of this disease are to be briefly mentioned, which may have a decided influence upon prognosis and therapy as well as upon the duration of the disease.

Ancient medicine recognized the following terminations of inflammation:

1. *Resolution*; 2. *Exitus letalis*; 3. *Transition into abscess formation*; 4. *Transition into gangrene*; 5. *Transition into induration, or caseation*. With this list I also include in pneumonia, another, a sixth mode of termination:
6. *Delayed resolution.*

Termination in abscess and in gangrene is quite rare, although frequent enough to require consideration. In a dense hepatization and slow resolution, in the midst of the hepatized tissue, one as well as several abscess foci as well as gangrenous foci may develop (probably with the assistance of streptococci and in the case of gangrene necessarily also of bacteria of decomposition). The appearance of abscesses in gangrene is shown by renewed appearance of fever and the presence of foul-smelling (fetid) sputum. The development of these processes in different foci protracts the course of the disease decidedly and endangers the life of the patient by exhaustion and fever. Careful treatment, with the use of disinfecting (antibacterial) inhalations in the majority of cases is successful in saving the life of these patients so that they are restored to health. At all events, the therapeutic success in this realm has become decidedly more favorable in the last decades.

Delayed resolution, to the importance of which I called attention years

ago, shows itself in that, after the cessation of the fever accompanied with periodic slight rises of the same, the patient recovers, but very gradually, while the signs upon percussion and auscultation remain unchanged for a long time. This occurs most frequently in very debilitated persons and in very firm pneumonic infiltration. Young persons show this method of termination as frequently as older ones. With very gradual recovery, by and by the infiltration resolves, showing the well known phenomena (crepitant râles, slight muco-purulent sputum), and often only after several months may the patient be looked upon as convalescent.

The gravity of the situation in such cases depends upon the question whether a new affection (abscess or tuberculosis) does not hinder the resolution; this gives rise to fresh anxiety which can but slowly be disseminated by careful observation and treatment.

Most important is the termination of pneumonia in *induration* and *caseation* (*tubercular pneumonia*). We naturally look upon this tuberculous form as necessarily due to an infection with tubercle bacilli. The question is answered with much more difficulty whether the tubercle bacilli infection was present before the pneumonia or only occurred after pneumonia, with the onset of convalescence. Most probably both conditions are right. It is not unlikely that persons who are already tubercular may be attacked by a genuine pneumonia which runs a typical course and terminates by crisis. After running its course, resolution ceases, renewed fever occurs and a grass-green sputum appears in which sooner or later tubercle bacilli can be demonstrated. Probably the tubercle bacilli enter from old foci into the hepatized area, settle there and in this manner lead to a caseous pneumonia with a threatening course. The process probably unfolds itself in a similar manner in the other cases, regarding the recurrence of which there can be no doubt, when in the course of convalescence from pneumonia fresh tubercular contagion occurs.

Complications and Sequels of Pneumonia.—*Metapneumonic empyema*.—As is well known, in every genuine pneumonia, besides the pulmonary hepatization, the pleura is implicated. As a rule, without any decided disturbance this condition returns to normal after the crisis. Occasionally an exacerbation of the pleurisy with slight fever takes place after the crisis; even then cessation of the process and return to the normal may occur.

In not a few cases a further development of the pleurisy occurs, a *purulent effusion* taking place. The diagnosis of this condition to-day does not give rise to noteworthy difficulties; even where there is only suspicion, we make the diagnosis with certainty by means of puncture with a Pravaz syringe. If *pus* is found, the indication for surgical interference (thoracotomy with resection of the ribs) is present. The attempts which were made formerly to produce resorption, to await spontaneous rupture, or to use drainage, according to Bülow, have all proven unreliable, as there are no positive chances of complete recovery; it is, therefore, advisable to operate and perform thoracotomy at once.

Not infrequently greater difficulties are encountered in encapsulated pleural exudates, that is to say, those situated between two pulmonary lobes; but this is not the place in which to thoroughly discuss this condition.

Other sequels will be but briefly mentioned. I call attention particularly to *infectious nephritis* which may develop after pneumonia, as well as after other acute infectious diseases. This complication has been previously mentioned. The prognosis is a serious one. Not infrequently does recovery occur and not rarely after a severe course the condition enters the chronic stage. A *multiple (rheumatoid) arthritic affection* is rare after pneumonia.¹ To the most important and most numerous sequels belong *affections of the nervous system*, similar to those occurring after other acute diseases. I mention a variety of *neurasthenia* after severe affections, which may be very protracted and may even lead to the most intense psychological disturbances; further, multiple neuritis, myelitis, encephalitis, also a form of Landry's ascending paralysis are to be included.

A severe, fortunately rare, complication, or even a sequel, of pneumonia is *acute meningitis*, which is exceedingly dangerous to life. In general this severe complication is rare; during a period of epidemics of cerebro-spinal meningitis, we noted its intercurrent more frequently. Bacteriological examination in several cases showed diplococci which corresponded to the diplococcus pneumonia. I was the first to call attention to, and publish an observation of this kind in the year 1882.

Finally, *cardiac affections* must be considered. This complication is not frequent but is of very serious import. *Endocarditis* and *pericarditis* occur. Without doubt, also milder forms of these inflammations appear, which terminate favorably without giving rise to difficulties, or even consequent conditions. Not rarely, however, is there a purulent pericarditis and infectious (ulcerative) endocarditis. This form, already known to Bouillaud, has not only been observed upon several occasions in the bacteriological era, but has been investigated bacteriologically and experimentally. M. Michaelis (in his researches regarding immunization against pneumonia in my clinic) found after sudden death in a dog infected with pneumococci, an exquisite ulcerative endocarditis in which pneumococci could be demonstrated in the deposits upon the valves. In man also there are numerous analogous observations. The typical forms of this kind (with chills) almost all terminate fatally. Without doubt, as has already been observed, milder forms of benign endocarditis and pericarditis occur; but the prognosis of these complications is always a serious one. Five years ago in my clinic I observed a well developed case of this kind, which unfortunately terminated fatally. I shall give the clinical history of the case:

F. K., coachman, thirty-eight years of age, admitted upon June 23, 1899, died August 2, 1899.

History: Patient, whose parents died of maladies unknown to him, has had several diseases, in his fifth year true variola, but, later, in the main he was strong and healthy. Upon June 21st, in the evening, he was suddenly attacked with stitches in the left side of the chest, accompanied with chills and fever.

Status præsens: Patient is a powerful man, complains of stitches in the left side of the chest, of difficulty in respiration and cough. The face is markedly turgescient,

¹ Cave (Pneumonia Arthritis, Lancet, 1901) found in a case of pneumonia complicated by purulent inflammation of the shoulder joint, in the pus which was discharged by puncture, capsule diplococci which grew upon agar and blood like pneumococci.

the tongue is tremulous upon protrusion; the movements of the patient are hasty and restless. Pulse 104, respiration 32, temperature 103.1° F. Upon the left posteriorly, in the area of the lower lobe, dull note upon percussion with loud bronchial breathing, expectoration scant, serous, slightly yellowish. Some albumin in the urine.

June 24th Morning: Temperature 101.7° F., pulse 104, respiration 24; evening: temperature 104° F., pulse 114, respiration 32.

June 25th. Morning: Temperature 102.7° F., pulse 96, respiration 33; evening: temperature 103.6° F., but little sleep at night, patient was restless, however, without

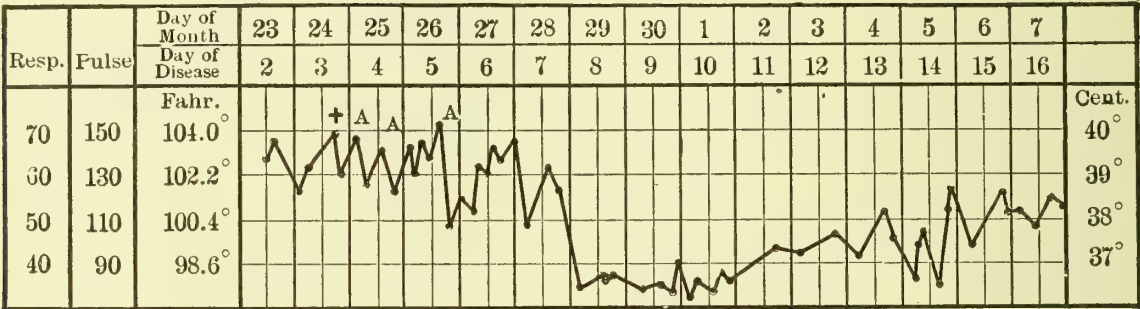


FIG. 39.

delirium. Upon the lungs posteriorly, upon the left very intense (from the angle of the scapula downward) loud respiration, few râles, sputum rusty (eleven o'clock a gram of antipyrin is given, patient's temperature is 103.2° F.; at one o'clock the temperature has fallen to 102° F., but rises again and at three o'clock it has reached 103.1° F.). Urine 1,300 cc., specific gravity, 1,020. At night an injection of 0.01 morphia.

June 26th. Morning: Temperature 103.4° F., pulse 108, respiration 48; evening: temperature 103.1° F., patient slept but very little during the night, was restless and delirious. To-day he is quieter but still semi-unconscious. Fascies composed, strength fairly good, the pulse particularly strong. Urine 900, specific gravity 1,020 (at five o'clock with a temperature of 104° F., one gram of antipyrin was given, the temperature fell to 100° F., and at seven o'clock is not higher than 101.3° F.); at night 0.01 morphia subcutaneously.

June 27th (sixth day of disease). Morning: Temperature 101.1° F., pulse 108, respiration 36; evening: temperature 103.2° F., pulse 114. Patient has not slept during the night, very delirious, he attempted to jump from the bed several times and had to be tied to the bed to prevent injury to himself and to other patients in the ward.

June 28th (seventh day of the disease). Morning: Temperature 100.6° F., pulse 104; evening: temperature 101.5° F., pulse 105. Patient was very delirious during the

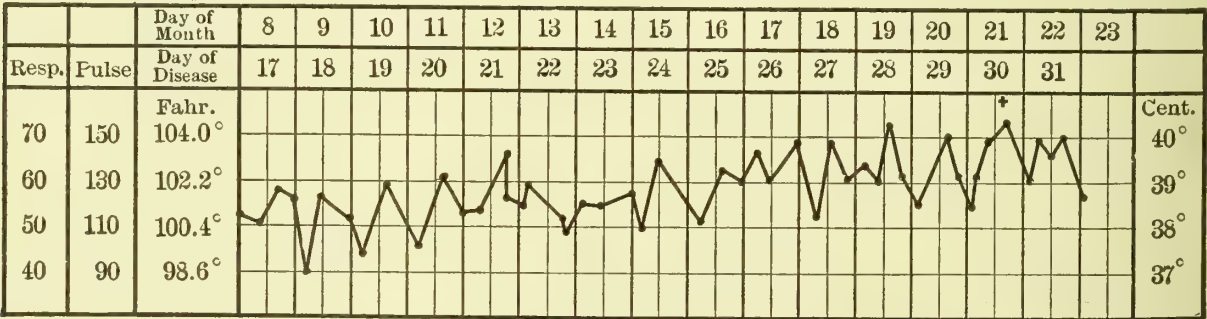


FIG. 40.

entire previous night and, therefore, was given chloral hydrate. At eleven o'clock 2.0, and at one o'clock 1.0, at half past five 1.0, and at eight in the morning 2.0; only to-day toward evening did the patient fall into a quiet sleep.

June 29th (crisis). Morning: Temperature 98.1° F., pulse 84; evening: temperature 97.5° F.

Patient during the last night has slept almost uninterruptedly, profuse sweating. To-day he sleeps a great deal (sopororous condition).

June 30th. Morning: Temperature 97.5° F., pulse 64; evening: temperature 98.1° F., pulse 72. Patient sleeps till noon, awakens and states that he feels quite well. Sputum scant, scarcely rusty; physical signs unchanged.

July 3d. Morning: Temperature 98.2° F., pulse 76; evening: temperature 99.5° F., pulse 84. Urine 1,500 cc., specific gravity 1,017. Patient to-day complains of cough and difficulty in respiration, further, of stitches in the left side. General condition not so good, appetite slight, felon upon the right index finger; this is opened by incision. Upon the following day (July 4th) the pains have disappeared.

July 5th. Morning: Temperature 99.5° F., pulse 108; evening: temperature 101.5° F., pulse 90. Patient complains of great lassitude. Upon the glutei two large furuncles have appeared, one of which is incised and discharges much pus. Patient conveys the impression of being quite ill and states that he feels sick. Consolidation in the lung is clearing up.

July 8th. Morning: Temperature 100.8° F., pulse 92; evening: temperature 101.7° F. Resolution of the pneumonia continues. *The incised wound in the furuncle still discharges pus. Patient conveys the impression of being very ill, he complains of lassitude and difficulty in respiration.* Marked sweating during the night.

July 11th. Morning: Temperature 99.5° F., pulse 96; evening: temperature 103.1° F.

July 12th. Morning: Temperature 101.1° F., pulse 94; evening: temperature 103.5° F., pulse 96. Urine 2,000, specific gravity 1,015. To clear up the cause of the fever two punctures were made into the pleura without success. The furuncles are healing well.

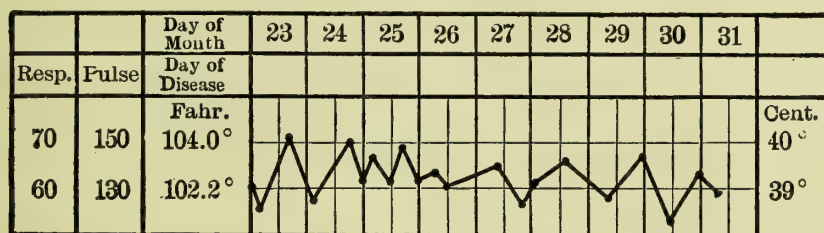


FIG. 41.

In respiration the left side does not dilate. Percussion over the left upper lobe gives a loud note as well as in the axillary region, there is loud full sound. *Cardiac dullness* very intense, extending from the left sternal border outward to the mamillary line, upward to the upper border of the third rib. Upon auscultation of the left lung good vesicular respiration all over, occasionally *crepitant râles* are heard. Auscultation of the heart shows two pure sounds, only at the upper margin of the left sternal border a very faint systolic murmur is heard (pericardial or endocardial?). Posteriorly to the left toward the middle of the scapula downward moderate dullness. Weak bronchial respiration with a few fine râles.

July 15th. Morning: Temperature 100.4° F., pulse 100, respiration 18; evening: temperature 103.2° F., a loud systolic murmur heard over the heart.

July 17th. Morning: Temperature 103.4° F., pulse 108; evening: temperature 103.4° F., pulse 112. With unaltered cardiac dullness to-day for the first time at the left sternal border, a *blowing diastolic* murmur can be heard. At the right sternal border the diastolic murmur is much softer, the diastolic sound can be heard. Over the carotid there is a weak systolic murmur with a distinct diastolic sound.

July 18th. Morning: Temperature 100.8° F., pulse 112; evening: temperature 103.2° F. The *diastolic murmur* to-day is plainly to be heard over the aorta. At the apex of the heart there is a systolic murmur. Subjective condition bad. Patient complains of pains over the entire body. At the left border the *diastolic murmur* is plain. Upon the skin of the chest numerous punctiform fresh hemorrhages. Hand, ears and feet free from emboli. Patient has several times had a sensation of coldness and trembling. Ice-bag ordered placed upon the cardiac region.

July 20th. Morning: Temperature 101.7° F., pulse 84; evening: temperature 102.4° F., pulse 108. Subjective condition bad. Patient complains of pains over the entire body. Pulse rapid, strong. At noon several chills occur lasting from 10 to 15 minutes.

July 21st. Morning: Temperature 101.1° F., pulse 90; evening: temperature 104.4° F., pulse 96. Urine 1,100 cc., specific gravity 1,020. Patient is somewhat apathetic, complains less, without being unconscious. *Diastolic murmur* at the left border of the sternum distinct but weaker than yesterday.

July 22d. Morning: Temperature 102.4° F., pulse 96; evening: temperature 103.6° F., pulse 112. Fresh purpura on both arms. In the heart a systolic and diastolic murmur. *Pulsus celer et altus*, pulsation of the carotid.

July 25th. Morning: Temperature 103.4° F., pulse 100; evening: temperature 102.6° F., pulse 108. Patient quite apathetic. No change in the heart. Ordered: antipyrin with transitory results regarding the temperature.

July 30th. Morning: Temperature 100.9° F., pulse 124, respiration 40; evening: temperature 102.9° F., pulse 128. Ordered: antipyrin. Increasing emaciation, mind no longer clear. Examination of the blood shows no leukocytosis.

August 2d. Exitus letalis.

The autopsy (Dr. Oestreich) shows: Endocarditis ulcerosa valv. Aortae et Mitralis. Dilat. et hypertrophia Cordis. Infarct. hæmorrh. renum, lienis et intestini tenuis. Multiple cutaneous hemorrhages.

The right ventricle is dilated, trabeculae slightly flattened. The wall of the left ventricle is about 1.5 cm. in thickness; upon the middle aortic valve there is a coagula of yellow color, permeated by fresh red areas about the size of hazel-nuts. Papillary muscles show a yellowish discoloration. Spleen is tough, yellowish-gray.

Bacteriological examination: Smear preparation from recent section from the endocardial proliferation, contains profuse lancet-formed diplococci.

Agar cultures (four tubes from the fresh-cut surface) show upon the next day, besides contaminations, typical colonies of pneumococci.

Animal experiment: A piece of the ulcerated valve crushed in sterilized bouillon; of this emulsion, two rabbits are subcutaneously injected, one with 2 and the other 3 ccm. Both die, one after three, the other after five days. In the blood of the heart of both, profuse pneumococci can be demonstrated.

It still remains for us to describe the **various forms of pneumonia**.

The numerous cases of pneumonia, in spite of great analogy, still show many variations, so that it has been thought well to differentiate various groups and forms of pneumonia. This is all the more justifiable as, with the variation of the appearance and course, frequently different etiologic factors or a varying predisposition are to be considered, and, further, the fact that they are combined with different dangers and deviations in course, requires the application of various therapeutic investigations.

To the oldest grouping of this kind belongs the differentiation of *sthenic* and *asthenic pneumonias* (M. Stoll's *bilious pneumonia*), which Leichtenstern has again taken up and advised. It is true, from this differentiation some important therapeutic conclusions may be deduced, nevertheless, I do not believe this division to be practicable any longer and, therefore, it is impossible to carry out, as both forms are due to the same pathogenic agent (the diplococcus lanceolatus).

Finkler, in his thorough work, *Acute Pneumonia as an Infectious Disease* (Wiesbaden, 1891), from a bacteriological standpoint differentiates three forms: 1. *Fibrinous pneumonia* (pre-eminently, perhaps exclusively, due to A. Fränkel's diplococcus pneumonia); 2. *Acute bronchopneumonia* (diplococcus and other bacteria); 3. *Acute cellular pneumonia* (pneumococci and streptococci).

Further separation of the pneumonia forms arises from a particularly practical reason and cannot be referred dogmatically to definite principles. I differentiate—with the majority of authors—the following forms:

1. Regarding *age* and *sex* of the patient, *pneumonia of children and pneumonia of the aged*.

The former, *pneumonia of children*, has always been separated, it occurs as bronchopneumonia, does not have such a psychical course and may be very protracted. Probably its etiology is also due to the diplococcus of pneumonia.

Pneumonia of the aged requires special consideration on account of the many peculiarities in the symptoms of the course and on account of the peculiarities of the affected individuals. Prof. L  moine has described the condition fully (Le Nord m  dical, Ao  t, 1900).

In old persons, as a rule, the onset of pneumonia is also ushered in by a *chill*. The pulse at first does not rise above 100, the dyspnea is moderate, cough is not frequent, expectoration is slight, rarely hemorrhagic. The temperature rarely rises high, 104   F. The signs upon auscultation and percussion are the general ones; occasionally, however, no physical signs can be determined upon auscultation and percussion except circumscribed crepitant r  les. The protracted course is to be feared in that strength declines and occasionally cardiac weakness most suddenly appears. The *therapy* should consist in diminishing the flow of blood to the lungs, quieting the respiration, administering heart tonics, and increasing general strength. Tonics and expectorants are to be given: ammonium acetate, ether; alcohol (as wine) cannot be dispensed with. Musk, strychnia and nux vomica facilitate expectoration, by their action upon muscular tissue. Ice is to be avoided ("old persons do not bear ice," Pye-Smith). The common absence of signs of pneumonia in the aged is also emphasized by other authors, so that not infrequently death occurs suddenly and unexpectedly.

Osler (Baltimore) says: Pneumonia is a common cause of death in the aged. Among 10,000 persons living at the age of seventy-five years and over, 95 are attacked by pneumonia. Often pneumonia of the aged is latent and there is almost an absence of characteristic symptoms. Death occurs unexpectedly, almost suddenly. Charcot also points to the fact that in the aged the severest diseases may run their course without symptoms; apparently, death has occurred unexpectedly and suddenly. The autopsy in such cases not rarely shows a pneumonia in the stage of suppuration.

In regard to pneumonia of the aged, Sir William Gull remarked as follows: The aged frequently die of pneumonia without showing symptoms.

Regarding *women*, I must remark that in general, *pneumonia in the pregnant woman* is to be feared, as it not rarely leads to abortion or premature birth. Artificial interruption of pregnancy comes into question; however, it had better be avoided. The prognosis is not so bad as was formerly supposed.

2. Regarding *constitution*, it is to be remarked that the prognosis of pneumonia is decidedly influenced by it. Thus, pneumonia runs a most favorable course in youthful, strong, rather thin individuals, also weak, thin persons bear the disease relatively well. *Pneumonia of the obese* is a severe disease. Usually there is distinct dyspnea and a conspicuous predisposition to cardiac weakness. The course of the affection is always severe, and with relative frequency death occurs from cardiac asthenia. The therapy endeavors to ameliorate respiration by purges, withdrawal of blood (venesection), and by giving relatively small amounts of nourishment, but undernutrition must be avoided

and alcohol is necessary. Oxygen inhalations, analeptica and heart tonics are advisable. Fat patients who have dyspnea lie quite horizontally and usually cannot bear a raised, reclining or a sitting posture. The *pneumonia of anemics* is also severe. Especially dangerous is *pneumonia in an individual with scoliosis* or with *arteriosclerosis*; the former on account of the increased difficulty of respiration, the latter on account of insufficiency of the heart.

Of other constitutional anomalies, there is to be mentioned the serious prognosis of *pneumonia in drunkards*, and the dangers of pneumonia in a previously tuberculous individual. The *pneumonia occurring in nephritics*, as well as in *gouty individuals*, is very dangerous. Emphysematous individuals attacked by pneumonia are in great danger, as are also those suffering from affections of the heart.

3. *Pneumonia* not rarely occurs in connection with other *infectious diseases* or attacks the patient simultaneously. The prognosis in these cases varies, but for the most part it is very serious. Bacteriologically-mixed infections occur. The best known mixed infections of pneumococci are those with the *bacillus of influenza and streptococci*. The first-named mixed infection brings about the peculiar condition which is known as *influenza pneumonia*. Regarding this disease, I may refer to the article by Prof. Fürbringer.¹

Pneumonia also occurs in connection with other infectious diseases, but everywhere with a serious prognosis. Pneumonia in the later course of *enteric fever*, which is due to a mixed infection of pneumococci and typhoid bacilli, is well known; also pneumonia occurs in the course of acute chronic polyarthritis. Of the acute exanthemata, particularly measles, more rarely scarlet fever and variola, predispose to pneumonia. Recently in a severe gangrenous diphtheria, in a boy aged ten years (with a fatal termination), I observed a distributed course, with grayish red hepatization of both lungs. Formerly, intermittent *pneumonia in malaria* was much spoken of, but these associations do not appear to be clearly demonstrated. I myself have observed *pneumonia in relapsing fever*. *Deglutition pneumonia* in the comatose and the apoplectic is of complicated origin. A *vagus pneumonia* (after severance or paralysis of the vagus) is no longer accepted. This form belongs to *degutition pneumonia*.

Finally, I must mention *ether pneumonia* after narcosis from ether, which has been variously described in the last year (The So-called Ether Pneumonia, Dr. Fr. Lili, Practitioner, 1900). To this is to be added *dust pneumonia* (Dust Pneumonia, Alfred Hillier, Practitioner, 1900, pp. 304 to 306).

A further description of these manifold varieties is not necessary. The deviating course and the various therapeutic indications may readily be determined from the etiology.

PROGNOSIS OF PNEUMONIA

The prognosis of pneumonia is always serious, pulmonary infiltration in itself is a serious lesion which threatens life.

In its course and in its intensity it shows the greatest variation. In spite

¹ See this volume.

of this, it is a disease of *typical character*, in the majority of cases terminating by crisis which is followed by convalescence. It might, therefore, be thought that the prognosis in such a typical course would be determined with some certainty, and in reality the prognosis depends upon the question: Is a crisis to be expected and when will it occur?

Regarding the mortality from pneumonia, this varies in different years from 5 per cent. to 26 per cent.; even without apparent cause, a series of favorable cases alternates with unfavorable ones (Skoda). Magnus Huss, in his well-known monograph upon pneumonia, gives a mortality of 7.43 per cent. for 1851, 12.27 per cent. for 1843; Grisolle gives, in men 17.9 per cent. mortality, in women 32.5 per cent. In general, according to recent literature reports¹ the mortality is from 10 per cent. to 12 per cent.

This gives no point of support for the prognosis in the special case, we must, therefore, observe the individual state.

1. Pneumonia runs a most *favorable course* in strong adult men (soldiers, young men between twenty and thirty-five years of age). 2. *In women* the prognosis is less favorable. 3. Strong children of from six to twelve years of age bear pneumonia well and recover readily; younger children who usually have bronchopneumonia, succumb more easily on account of frequently repeated exacerbations. 4. Elderly, weak individuals, from forty years on, are more threatened, at most the aged rarely have severe forms but the course is often protracted. 5. On account of *constitutional peculiarities*, the *obese* are most particularly endangered, for the most part on account of the increased difficulty in respiration, as is also the case in individuals with skoliosis, arteriosclerosis, and alcoholics, then anemics, ill-nourished persons or such as have been injured by previous disease. I have called attention to all these cases in describing the various forms of pneumonia. As usually in the first days the disease appears relatively mild and as the severity of the case only becomes evident upon the fourth or fifth day, the question arises, what points of support have we for expecting a favorable course and early crisis.

Favorable signs are: Distinct but moderately developed symptoms and signs, typical course of the fever, moderate frequency of the pulse (90–110–120 beats per minute, not over); strong, high, regular pulse; regular respiration of moderate frequency without subjective dyspnea. No decided complaints, relatively quiet condition, fair intake of nourishment and absence of complications.

The appearance of the crisis, or at least amelioration of the symptoms, may soon be expected if upon the fifth or sixth day the condition is improved, necessary, moderate sweating occurs, *herpes* appears about the mouth, nose and face, no dyspnea is present, and there is relatively good respiration, no decided condition of weakness, and no *cyanosis*. Mild delirium and jaundice do not markedly increase the seriousness of the prognosis if the expectoration is feebly rubiginous (lemon yellow) or without color, less tough, whitish, and rich in cells.

Of *unfavorable import* are, great severity of the symptoms from the onset

¹ Compare Transactions of the Congress for Internal Medicine. Wiesbaden, 1900 (Korányi and Pel).

of the disease, great extent of the pneumonia, increasing dyspnea, immobility and apathy of the patient, continued high temperature and a pulse frequency above 120. Compared with this, the character of the sputum is of no decisive importance. The appearance of any one of the above-mentioned complications is naturally of unfavorable prognosis.

The *fatal outcome* is sometimes due to pulmonary edema (in those areas not attacked by pneumonia); in the greatest majority of cases, however, death is due to insufficiency of the heart (Jürgensen) or oligemia and exhaustion of the respiratory muscles (Bollinger).

Symptoms which denote immediate danger are, apathy in the facial expression, cyanosis, great weakness, with a rise in the pulse and respiratory frequency, serous expectoration (foamy, thin fluid, red or blackish-red)—(prune juice expectoration—Ed.), piping respiration, onset of tracheal râles.

In connection herewith, I shall cite the opinions of some medical authorities regarding the most important prognostic signs:

Canstatt: The fatal outcome of pneumonia may occur in any stage, by suffocation, pulmonary paralysis, cerebral pressure, strangulation, coagulation of blood in the heart. The condition is serious if the patient is only capable of breathing when in a particular position, when anxiety and dyspnea reach a high grade, when there is a pallid (lead-colored) appearance of the face, and when severe delirium and coma occur.

Jürgensen: The danger of pneumonia is cardiac weakness, death is due to cardiac insufficiency. *Acute* cardiac insufficiency may appear at once upon the patient sitting up quickly; he falls over dead or he dies after a brief death struggle or with a gradual sinking.

Pye-Smith (London): The greatest danger is from dyspnea as a result of the extension of the pneumonia, overburdening of the heart, arterial anemia; at other times death is not due to suffocation but to a weakening of the respiratory muscles and exhaustion as the result of the action of the high temperature upon the heart.

PATHOGENESIS AND ETIOLOGY OF PNEUMONIA

At present we count pneumonia among the infectious diseases due to a specific bacillus, the *bacillus lanceolatus*, or *diplococcus pneumoniae* (A. Fränkel).

Before entering upon the bacteriology of this affection, I shall give a concise review regarding the various opinions which preceded the present one, as I have done in the other chapters. And I do this to briefly sketch the peculiar course of development of medicine, which may be readily followed, particularly in the case of pneumonia; on the other hand, also to show that bacteriological investigation, as high as I place it and as fruitful as it has shown itself, is not the entire science of medicine to-day, but that also experience at the sick bed has an important place.

Ancient medicine did not much concern itself with the etiology of disease, and physicians, therefore, in that period as well as in the Middle Ages, applied to it various philosophical theories. Only at a later period (eighteenth to nineteenth century) more distinct views appear. For the greatest part the

cause of pneumonia was looked for in climatic conditions, and a decided etiological influence was attributed to cold and winds. During the time of Sydenham, Boerhaave and the first Vienna Clinic, it was included among the inflammatory fevers, the fever as synochia, and designated *synochial fever*. Maximilian Stoll differentiated the bilious form of pneumonia, which was also described as *asthenic pneumonia*, and differed from the erethic character of asthenic pneumonia by weakness, stupor and tendency to decomposition. L. Traube for a time differentiated winter and summer pneumonias, the former as an erethico-asthenic, the latter as the asthenic form.

As a result of this, the *geographical* distribution of pneumonia, as well as its sporadic and epidemic appearance, was investigated.

Pneumonia is one of the most widely distributed of diseases, it occurs in all *latitudes* and in all *climates*; it is, however, more frequent in cold climates and cold seasons than in the warmer.

The *weather* is of influence, moisture, when accompanied with rain and wind, favors the appearance of pneumonia; dry summer heat does not favor pneumonia. Among the most important causes, refrigeration must be reckoned, especially repeated refrigerations. It is also worthy of mention that etiologically, besides *refrigeration*, *injuries from blows* and *shock* were early included in the etiology; injuries, fracture of ribs, contusion of the thorax, prolonged exertion, were designated by Wunderlich as important etiological conditions.

This etiology was almost forgotten, when M. Litten rediscovered it, so to say, designated and described the condition as *contusion pneumonia*. At the present time, in connection with accident insurance, this question is of particular interest. According to the present scientific views, a contusion pneumonia must certainly be recognized, i. e., the development of pneumonia by blows, etc., without any other previous cause being active. The pneumonia would not have developed if there had been no trauma. Naturally, also in these forms of pneumonia, the pneumococcus is the pathogenic agent.

Of great importance were the investigations regarding the *epidemic appearance* and the *contagiousness of pneumonia* which immediately preceded the bacteriological investigations.

Wunderlich long since, in his Special Pathology and Therapy, which is even of value to-day, spoke of a sporadic and of an epidemically appearing pneumonia. This occurs frequently in the spring, most rarely at the height of the summer. E. Klebs called attention to the fact that the pneumonia which occurs in Switzerland during the time at which the snow begins to melt, and is there designated as *Alpine stitch* (Alpenstich), shows an epidemic condition throughout. In Florence, during the year 1877-78, as well as in Erbenheim in 1882, an epidemic of pneumonia was observed; inside of twelve days 54 cases of pneumonia occurred, 5 of which died.¹ Further, epidemic appearance of pneumonia in barracks (Magdeburg, 1873-74, 70 men being attacked = 13 per cent. of soldiers living in these barracks), in prisons (Dr. Kerschensteiner observed 161 cases in Amberg in 1880); finally, house epidemics have been

¹ See the valuable work of M. Mendelsohn: "Die infectiöse Natur der Pneumonie." Zeitschr. f. klin. Med., 1881.

described (Müller, Deutsches Arch. f. klin. Med., 1877). Direct contagion has also been observed and described (Kühne, Knoevenagel, Contagious Pneumonia, Deutsches Arch. f. klin. Med., 1876). Wymann in Boston observed the appearance of several cases of pneumonia in one family. I could report analogous cases of contagion from my own experience. Contagion may occur directly, Eichhorst also believes in contagion by a third person.

The next important advance in our knowledge regarding the nature of pneumonia is due to *bacteriology*. E. Klebs appears to have been the first who recognized schizomycetes in hepatized lungs,¹ he called them *monas pulmonale*; also in the fluid of the cerebral ventricles of pneumonics he found the same schizomycetes. Eberth, in 1881, in a case of pneumonia and meningitis, found small, almost round bodies, also twin shapes. In 1882, Dr. C. Friedländer (Berlin),² who unfortunately died so early, described cocci of an elliptical shape in the alveoli and the lymph spaces of the interstitial connective tissue. In culture he obtained peculiar forms, which he described as nail cultures; his further studies lost in clearness. Besides this coccus, he described and cultivated a second bacillus.

In 1884, in a case of pneumonia, by puncture with a Pravaz syringe I was able to withdraw blood from the hepatized lung and to demonstrate numerous pneumococci in it.³ In the animal experiment with fluid from the lung and sputum (in rabbits), we did not succeed in producing pneumonia (only purulent pleurisy a few times); the animals died rapidly without local affection. Griffon and Cavatus also inoculated rabbits with sputum and rapidly produced septicemia. Simultaneously, Prof. A. Fränkel, at that time assistant in my clinic, conducted careful studies regarding the pathogenic agent of pneumonia, the results of which were reported at the Congress for Internal Medicine. He described the pathogenic agent of pneumonia as a diplococcus of oval (lancet) shape; the cultures only exceptionally presented themselves in the manner of Friedländer's nail cultures.

Almost simultaneous descriptions of pneumococci were published in Paris by Netter, in Vienna by Weichselbaum, in Italy by Uffreduzzi, Salvioli, Bordoni.

Since that time it is a well determined fact that the pneumococcus, which often in several links resembles the streptococcus form, the individual links of which are of a lancet shape, is the actual pathogenic agent of fibrinous or essential pneumonia.

The *diplococcus pneumoniae* (pneumonia micrococcus, A. Fränkel, micrococcus of sputum septicemia, diplococcus lanceolatus, lancet-formed diplo-meningococcus, diplococcus lanceolatus Pasteuri) properly does not belong to the cocci. Its parts which usually occur in pairs are somewhat lengthened and at the ends are distinctly pointed like a lancet. The organism is immotile. Lying in the tissue in the pneumonia of man, or in the organs of trial animals, the diplococcus (that is, bacillus) shows itself to be surrounded by a distinct capsule. In artificial cultures the organism shows no capsule.

¹ Beiträge zur Kenntniss der pathogenen Schizomyceten.

² Die Schizomyceten der Pneumonie.

³ Dr. M. Mendelsohn (l. c.) withdrew blood from the hepatized lung of horses; in two cases he found diplococci resembling those found in man, but smaller in size.

The diplococcus pneumoniae grows upon artificial culture media but only at a high temperature, below 22° C. no growth occurs. It grows best at about a temperature of 35° C. The culture media must be feebly alkaline. Upon the surface of agar and blood serum, the diplococcus pneumoniae forms a very fine coating, appearing as if composed of individual dew-drops which remind us of cultures of erysipelas cocci. Agar cultures perish in a few days after they are no longer pathogenic in animals; bouillon cultures are somewhat more durable.

The diplococcus pneumoniae is pathogenic in our trial animals, particularly in rabbits, but also in guinea-pigs and mice. If a rabbit is injected beneath the skin with a fresh virulent bouillon culture the animal perishes in from one to two days from a typical septicemia. The spleen is markedly swollen.

The diplococcus stains with the usual watery alcoholic staining solutions, the protoplasmic body is colored dark, whereas the capsule only takes on a slight color. The organism also stains according to Gram. In the latter method, however, only the protoplasm body remains colored, whereas the capsule decolorizes completely.

A number of proofs have been advanced, favoring the view that Fränkel's diplococcus is actually the causative agent of lobar croupous pneumonia: First, the diplococcus may be demonstrated in the sputum in more than three-quarters of the cases of pneumonia; further, the pneumococci are found in the blood of some patients with pneumonia (according to recent reports, in many, or even all). Then the pneumococcus may be demonstrated in other localizations of the diplococcus, thus, above all, in pneumococcus angina, which often shows the characteristic general symptoms of pneumonia (the sudden appearance of the fever, critical defervescence, etc.). Finally, in the blood of persons who have recovered from typical pneumonia, specific protective substances have been determined, which are capable of immunizing animals against a pneumococci infection (G. and F. Klemperer, Emmerich, and others).¹

The direct proof of the etiological significance by means of the *animal experiments* meets with difficulties in so far as our usual trial animals—rabbits, mice—are much more susceptible than is man to the pneumococcus, as a rule, succumbing to the septicemic general infection, a *localized* disease being very difficult to produce in them. Nevertheless, success was attained by inhalation of pneumococci, especially in the dog which is less susceptible, true pneumonia being produced by the *experiment*.

Some authors look upon severe pathogenic agents as the cause of pneumonia, and Friedländer has already described two forms.

However, genuine (essential) pneumonia is such a sharply characterized, I might say individual, disease that it can only be produced by one distinct pathogenic bacillus. In this sense I am a positive exponent of the view of the *uniformity of genuine pneumonia*, and this opinion is probably that of most pathologists and clinicians to-day. This uniformity does not exclude

¹ Agglutination should also be thought of here, which Griffon (Thèse de Paris, 1900) first studied. Dr. Huber in my clinic has confirmed this remarkable phenomenon. Agglutination can only be determined by cultivating the pneumococcus in the blood serum of the patient at a temperature of 37° C. The coccus develops in clumps which consist of heaps or wound chains of the coccus.

In pneumonia, agglutination can only be determined at the end of the febrile stage, best on the day after the crisis. In pneumococci septicemia, agglutination is absent or it is very indistinct.

the occurrence of *mixed infections* (pneumococcus with other pathogenic bacteria, for example staphylococci, streptococci, influenza bacillus, etc.) which may decidedly modify the anatomical picture as well as the symptomatology and the course of the affection.

The question of *mixed infection* is by no means fully decided as yet; this is especially true of mixed infection with streptococci. Not a few authors recognize a streptococcus pneumonia, but that a streptococcus alone is capable of bringing about a *fibrinous* pneumonia is to be very much doubted. If streptococci are found together with diplococci in pneumonia, the question arises whether both simultaneously mix and produce pneumonia, or whether the streptococcus appears later and causes suppuration.

This property of the two bacteria of following each other is seen most frequently in metapneumonic empyemata; if we aspirate early enough we usually obtain the characteristic diplococcus, but soon afterward, and occasionally from the onset (empyema is a quite late sequel of pneumonia), the diplococci are mixed with streptococci. If the empyema exists for a longer time and has become decidedly purulent, exclusively or almost exclusively streptococci are found.

In the influenza epidemic of the year 1890–91 I saw a pneumonia which ran a fatal course. The lung was partly in a condition of gray hepatization with partial softening. Besides diplococci, the microscopic examination conducted by Dr. Bein showed streptococci filling the small vessels of the hepatized area throughout a great extent.

Lately, Dr. Huber, in my clinic, in the summer of 1901, in which very few pneumonias occurred, in one case, in a pale rusty sputum, demonstrated streptococci predominating over diplococci. The cultures taken from this proved nothing. Of the mice inoculated with the sputum, as many died from streptococci as from diplococci.

Also, the appearance of *pulmonary abscess* after pneumonia raises the suspicion that diplococci and streptococci are frequently implicated together in mixed infection in pneumonia.

Still other mixed infections have been described. In a pneumonia occurring in enteric fever v. Stählein (Centralblatt f. Bakteriologie) found pneumococci as well as typhoid bacilli. The mixed infection with influenza bacilli (influenza pneumonia) must also be remembered.

The occurrence of pneumonia in the course of many infectious diseases is not rare, for example, measles, acute articular rheumatism, relapsing fever and even malaria. In how far mixed infections are present cannot be decided. It is not unlikely that these are due to *secondary infection*.

We must still mention the appearance of tubercle *bacilli in the sputum*, which further leads to caseous pneumonia. Two possibilities are present. Either the tubercle bacilli were previously present in the body before the pneumonia developed or they appeared in the course of pneumonia. Both views are tenable; it is difficult to say which is more frequent and which more likely.

In thus recognizing the diplococcus of Fränkel as the actual and only pathologic and typical agent of croupous pneumonia, this by no means completely clears the question of the etiology of pneumonia. How does the bac-

terium reach the lungs and in what manner does it unfold its activity there? An exhaustive answer to these questions is impossible. Only this much may be said: The pneumococcus normally lives in the oral cavity, it may often be determined in the mucus of the pharynx of healthy individuals in large numbers, also in the normal larynx a few bacteria may sometimes be found; below the glottis, however, in the healthy there are no microorganisms, *the bronchi and the pulmonary tissues of the healthy person are free from germs*. Therefore, in general, for the occurrence of pneumonia an *accidental* indirect cause must be active, we have learned to recognize such auxiliary agents in refrigeration, in trauma—which give to the diplococcus in the oral cavity the property of moving downward into the air passages and there giving rise to inflammation.

That this inflammation shows a particular character (*fibrinous pneumonia*) may depend upon the specific activity of the poison formed by the pneumococci (pneumotoxin); but chemically, in regard to this, nothing reliable has as yet been determined.

Two questions of particular interest have arisen as to the course of the process, the crisis and the resolution.

1. After recovery from the disease what becomes of the diplococci developed in such extraordinary numbers in the pneumonic lung? If pneumonic lungs are examined at the acme of the disease, in the majority of cases the entire infiltrate is thickly permeated with pneumococci; they lie between the blood corpuscles and the lymph cells. In other cases, if the patient dies in the stage of resolution few or no cocci are found. Have they been coughed up or how have they disappeared? The amount of expectoration in pneumonia is frequently very slight, usually quite scant. The greatest number of pneumococci are dissolved locally. This view is no longer held to-day as we know from other bacteria that they are rapidly dissolved by the immune products contained in the leukocytes and thus disappear (for example cholera bacilli in the abdominal cavity after the injection of immune serum). These immune products in pneumonia are formed in the bone marrow and transported by the leukocytes into the diseased lung where they destroy and dissolve the pneumococci.

2. Does immunity occur at the crisis? We consider that in the critical defervescence of the disease, the leukocytes that carry the antibodies accumulate and simultaneously reach such a high degree of immunity that the activity of the toxins is lost almost suddenly. Much favors the fact that *this immunization is a local one*, occurring inside of the area of hepatization; there the dissolution of the pneumococci occurs; this view is favored by the investigations of Fr. Müller. However, a certain antitoxic action is present in the blood, particularly in the blood serum, of pneumonia convalescents (G. and F. Klemperer, Huber and Blumenthal); therefore, with the crisis, not only a local immunity occurs in the lungs but also an incomplete one in the blood.

In regard to how long this immunity lasts, nothing certain can be said as yet. At this point I may refer to the older clinical experiences, which teach that, in the majority of cases, pneumonia only occurs once in the life of a patient; at the same time, however, cases have always occurred in which the

patient after the first pneumonia has shown a conspicuous predisposition to a fresh attack. Some persons, for instance adults, have been attacked six or eight times, and even ten to twelve times, by pneumonia of varying intensity, and still no diminution in severity was to be observed; on the contrary, some persons die in the last attack, a proof that the disease and the toxic action at least had retained its old intensity.

THE TREATMENT OF PNEUMONIA

In the treatment of pneumonia, clinical medicine finds itself in a transitional stage, which as such presents many points of uncertainty and for this reason is subject to the view-point of the individual physician. We have not as yet a definite method of treatment. Particularly that positive method of treatment, which now is our endeavor and goal, for the infectious and bacterial diseases is wanting, we still lack a specific therapy fashioned after Behring's serum therapy for diphtheria. Nevertheless, the therapy of pneumonia is based to-day upon a much firmer foundation than even in former times, and consists of well tried, scientific indications.

The termination of the last century inspired the compilation of a comprehensive retrospect regarding the progress of medicine; in this, pneumonia has also been particularly considered. The literature of foreign countries (America, England, France) has already presented such retrospective compilations which all deserve notice. In Germany several have also been published. Besides the work of Aufrecht upon pneumonia, in the large Nothnagel edition, I mention the two excellent compilations regarding the treatment of pneumonia which Korányi and Pel presented to the Congress for Internal Medicine in 1900. In connection with the discussion provoked by these, they show in an excellent manner the standpoint which clinical medicine has taken regarding the treatment of pneumonia to-day. The article on pneumonia by Liebermeister in the Ebstein-Schwalbe Handbuch should also be mentioned. Above all, however, I must mention the recent excellent work of my distinguished colleague, Prof. C. Gerhardt,¹ which in a masterful manner concisely and exhaustively presents the subject.

I shall have an opportunity to refer to the views and expressions of these authors repeatedly.

The standard therapeutic principle to-day for pneumonia was first expressed by Prof. Jürgensen in Tübingen. He says: "If pneumonia is an infectious disease it must be treated according to the same fundamental principles which experience has proven valuable in other infectious diseases."

These are the same principles which have been formed for the treatment of the acute exanthemata, erysipelas, and partly also for enteric fever. They depend upon reserving and assisting the powers of the patient, the physical as well as the psychical, by care in rendering the course of the disease as mild as possible, so that the patient victoriously recovers from the struggle with the disease. For this purpose we not alone need an exact knowledge of the entire course of the disease and the variation of its symptoms, as well as the

¹ Bibliothek v. Coler, Bd. x, 1902.

dangers which are present, in order to prevent every disturbance and aggravation of the course, but of many, perhaps not decisive, but still important measures and methods to moderate the dangerous symptoms and to supplement the powers of the patient. This course of treatment makes necessary for its purpose the adoption of various methods, as well as the proper use of the same at the right time. For the most part they do not depend upon active remedies but upon many little ameliorations and supports which, however, combined may be of the greatest decisive importance.

I shall describe the individual methods and remedies, their value and their indications according to my experiences and views in as decisive a manner as possible, and in conclusion I shall indicate a plan of treatment in so far as practicable. From this it will be seen that not much can be advocated with absolute certainty, for a great deal rests upon the peculiarities in the course of the acute disease, their points depending upon the individual characteristics of the patient, much also upon the physician who is treating the case. The diverse methods of treatment, and the remedies at our disposal are simultaneously the various weapons with which we can combat the enemy; although which of these and at what time they are to be particularly used, cannot be very definitely stated. As the commander-in-chief who is in possession of a variety of weapons alone decides upon their position and employment, so it is left to the judgment, experience, and we may add, the genius of the physician to utilize the approved methods at hand with skill and foresight, so that a victory may be gained under desperate circumstances.

A *proper comprehension* of the therapy of pneumonia in use to-day can only be obtained if a retrospect regarding the historical development of pneumonia therapy is considered. I shall, therefore, begin the description with a review. The history of the treatment of pneumonia as it has successfully developed is a true classical example of the mutability of medical doctrine and of the variations of all therapeutic methods which are based upon theories. From a retrospective observation, a conclusion can be drawn that our ancestors who endeavored to combat the nature of the disease, which they misunderstood, overestimated their remedies in a curious manner, but that also very much regarding prognosis and therapy was observed with extraordinary acuity.

My late friend and colleague, Prof. O. Frentzel, upon May 18, 1887, in the Society of Military Physicians, delivered an interesting and learned lecture (The Treatment of Croupous Pulmonary Inflammation), in which he described the rapid change of authority and methods in the treatment of pneumonia, as compared with the conditions existing about the middle of the previous century. Said he: "The mighty change which has occurred in therapy in the last thirty years proves most conclusively that the entire genius epidemic of pneumonia has become a different one. Thirty years ago Schönlein treated almost every pneumonia by venesection, whereas this method had already been abandoned in Vienna and indifferent therapy employed. At both places favorable results were claimed. Then L. Traube about the end of the middle of the century called attention to the fact that the pneumonias of summer had a decidedly different character from those of the winter. The former bore venesection, in fact all withdrawal of blood, very badly, the latter very well. The use of digitalis, etc., has also been more and more abandoned.

Remedies which were in vogue in former times, like tartar emetic, etc., have been discontinued for a long time," etc.

From this variation just described regarding the value of methods of treatment, we have gradually worked up to sound principles. Nevertheless, to properly appreciate what is done to-day a brief knowledge of the historical development is necessary.

Historical Retrospect of the Therapy.—Medicine of antiquity presents a number of errors in therapy, but also—as well as in symptomatology—a series of conspicuously beautiful and fruitful view-points. In Hippocratic medicine, as well as in the medicine of the Talmud, venesection and the law of crisis play the main rôle. As a rule, decided amounts of blood were withdrawn (from the arm, from the foot, from the tongue), blood was allowed to flow until it became light red, or vice versa until it began to be blue. As a general rule, all active measures were withheld up to the fifth day of the disease (sic!). Up to this period the general treatment of the fever consisted in warm washings, inunctions of oil, acid drinks, warm baths. From the fifth to the seventh day purgatives and venesection were employed.

Galen followed the teachings of Hippocrates. Venesection in his therapy also plays a great rôle, but he cautioned against its misuse. In children under fourteen years of age he forbade venesection. In pneumonia venesection, and at that in the arm of the affected side, was the principal remedy. Besides, purgatives (colocynth, hellebore) are indicated. In case of diarrhea, opium, hyoscyamus, further diaphoretics, honey-water, tisane, light diet and wine.

The celebrated Roman physician, Asclepiades, was opposed to venesection and he also limited the use of purgatives.

The treatment of pneumonia in the celebrated school of Salerno is noteworthy as described by Joh. Platerius: Dietetic measures play the principal rôle, warm air (heated in winter) is necessary, besides hemorrhage from the nose is to be produced by irritation of the nasal mucous membrane.

We find the therapy of pulmonary inflammation at the time of the first Dutch Clinic in Boerhaave's Aphorisms and the Commentary to these by his celebrated pupil, van Swieten (Part II, vol. ii, page 435). It (i. e., pneumonia) is cured: 1, by a favorable resolution; 2, by the expectoration; 3, by bilious diarrhea; 4, by thick urine containing sediment from the seventh day on. Then the breathing becomes slow, the fever lessens with sweating and marked hemorrhage from the nose (Aretæus) the crisis occurs. The disease requires rest of the body and of the mind, luke-warm, moist air, steam to the lungs or nose, mouth, feet and thighs, sparing diet, mild drinks, watery, starchy food containing saltpeter and honey. If a decided inflammation affects a previously strong healthy person, the following remedies are to be employed at once: 1, Rapid profuse, eventually repeated venesection; 2, steam baths permanently to the lungs, and frequently applied to the rest of the body; 3, diluted, softening, anti-inflammatory, cooling decoctions containing saltpeter, that is, anodynes in small amounts, frequently repeated, to be administered very warm; 4, the mildest, hot, damp clysters; 5, very scant diet consisting of anti-inflammatory fluids.

Maximilian Stoll, the exponent of the first Vienna Clinic, remarked as follows: The cure of the fever requires that the parts that are tense become

flaccid, and the fluid circulating in the parts be diminished. This occurs by profuse, repeated venesection, by softening fomentations, acid, cooling drinks, and a light diet, quiet of the body and of the mind, in fact by everything which is included under the antiphlogistic method. The cure must naturally be altered according to the varying conditions of the disease and of the severity of the same, as a remedy which is useful in one period of the disease may have an injurious effect at another period of the same disease.

Joh. Christian Reil (*Cure of Fever*, 1820) says regarding the therapy of pneumonia: "If it shows the character of synocha, the antiphlogistic method is always to be used; withdrawal of blood is absolutely necessary. After the first venesection the patient is usually relieved, but one venesection is rarely sufficient; besides venesection, cooling remedies, saltpeter, salammoniac, acids, mucilaginous drinks, clysters, hand and foot baths, and half baths are to be employed. Oil internally, half an ounce several times daily. Milk, spermaceti rubbed up with sugar. Rarely purgatives. Antiphlogistic régime: well-regulated ventilation, light bedclothing."

The celebrated English physicians of that time, Sydenham and Cullen, had their patients get up for several hours daily, a treatment that I, as a student, saw employed during the middle of the preceding century in Wolff's clinic.

Hufeland, whom we have previously quoted, designates the therapy of that time in the following manner: Venesection, tartar emetic, clysters are the principal agents; tartar emetic (with saltpeter) he regards as a true specific in this disease. Calomel with opium, senega and salammoniac. Much drink consisting of mucilaginous fluids. However, the varying character of pneumonia also requires different indications in treatment.

Canstatt, a contemporary of Schönlein, gives the following indications: The hyperemic lung is to be relieved of the amount of blood, for this reason withdrawal of blood in decided amounts from the arm of the affected side is indicated more than in any other disease. Usually venesection is repeated two to four times. Besides venesection, Canstatt advised local blood-letting (by leeches, wet cups) and wine of antimony (introduced by Rasori, and at that time designated as a decided advance in therapy; Rasori administered 1 to 2 grams daily), further, saltpeter (nitrum) for its antiphlogistic effect, calomel with opium, lead acetate, potassium carbonate. Digitalis is also mentioned by Canstatt but designated as not being indispensable; further, fomentations and inhalations, applications of wool in the yolk (warm oil inunctions).

During the time which followed, at the close of the eighteenth century, a transformation in medicine took place due to pathological anatomy, the development of physiology and the discovery of curative methods. Primarily, physiological medicine, which was inaugurated by Broussais, particularly regarding pneumonia, fell into the old footsteps and even advocated blood-letting increased to the limit of possibility (*Saignées coup sur coup*, *saigner à blanc*). This period still lasted a number of years, venesection still remained the sovereign remedy until Dietl in Vienna discontinued it. As a young physician I still saw some of the results of the Broussais school, for it was told me while I was attending a military manœuvre upon the Rhine that

a man had died there (in the neighborhood) of pulmonary inflammation although he had been bled four times.

Medicine at this time had attained a certain dogmatic firmness of which one might almost be envious. A stately structure had been erected but it was already felt that the foundation stood upon an uncertain basis.

Up to the middle of the previous century, in German Medicine it was looked upon as an unalterable article of faith that the treatment of pneumonia, in particular, represented a triumph of scholastic therapy.¹ Local and general blood-letting, saltpeter and small amounts of antimony² represented the indispensable measures of treatment for pneumonia.

In the meantime, differing opinions existed outside of Germany. In Italy Rasori had introduced the treatment with large doses of wine of antimony which was also accepted by Laennec and his pupils. Bouillaud expressed himself against the medicamentous antiphlogistic treatment. The infallibility of the medical pneumonia treatment began to sway and the adherents of rational medicine (Henle, Pfeiffer) took a stand against the necessity of the usual antiphlogistic method and showed that a large number of pneumonias recovered without withdrawal of a drop of blood, without a grain of saltpeter and antimony and without sweetened mercury, even that convalescence in such cases was more rapid.

This shattered the old historic theory of pneumonia. The previous certainty and authority gave way to innovations and doubts which varied in a lively wave-like manner and in the individual case opened the door to discretion, pessimism and illusion.

Upon this prepared soil the discourse of the Vienna clinician, Prof. Dietl, was planted: *Venesection in Pneumonia*, 1849, which was written with a sharp criticism demonstrating the inertness of venesection, and in which it was shown that without any positive treatment pneumonia at certain times ran a mild course, at other times a severe course, as with the previous scholastic treatment by venesection. Unfortunately, this critical analysis by Dietl was followed by a discouragement in therapy which had a very deleterious influence upon the course of medicine, in that it led to the therapy of observation (expectant treatment) and to pessimism, from which medicine worked its way upward exceedingly slowly.

Joh. Lukas Schönlein (1844 to 1860), the celebrated physician who founded the new Clinic in Berlin, was an adherent of expectant therapy, in opposition to the previous polypragmatic clinic (Wolff); and the extensive administration to the patients of his clinic of *solutio gummosa* instead of any drugs is even followed to-day. Nevertheless, he adhered a little to the old school.³ Pneumonia in his clinic was treated with venesection and

¹ *Kiesel*, *Die directe Kunstheilung in der Medicin*, 1852.

² How long this period of medicine lasted may be seen from the fact that the celebrated French clinician Trousseau, in his text-book, had written an article upon pneumonia, which contained almost nothing else but the praise of antimony in the therapy of pneumonia.

³ I remember a lecture in which he complained of the sparsity of the German pharmacopeia at that time. The present one they also called poor compared to the amount of the daily number of drugs which appeared.

digitalis. He practiced venesection (rarely two to four times) upon the sixth day of the pneumonia, and then upon the seventh day of the disease, not without pride, he showed his clinical students the patient in the state of defervescence, whom he had saved thereby. He also laid stress upon the latent urinary crisis. In convalescence, Schönlein administered emulsio chinata. I do not remember other drugs that were used in pneumonia besides the previously mentioned emulsio gummosa. I saw the use of tartar emetic and of calomel in pneumonia, in the second Clinic conducted by Wolff, naturally, also with apparent great success.

Digitalis belonged to those drugs which Schönlein introduced as a regular treatment in pneumonia, and at that by the administration of large doses of the remedy. After Schönlein, L. Traube accepted this therapy and added thereto his classical observations regarding the physiological and therapeutical investigation of digitalis, which occupied his time for a number of years. But also the digitalis therapy began to sway, and, under Traube's direction, I was able to observe how this remedy in large doses became dangerous, producing serious cardiac asthenia, particularly in time of the crisis and even giving rise to fatal cardiac paralysis; this corresponded with the results of the experimental investigations and later on led Traube to limit the use of digitalis in pneumonia and to reject it as the principal remedy.

The tendency which the treatment of pneumonia now assumed was in connection with the investigations regarding fever, which was stimulated by the physiology of body-heat (Dulong and Deprez), who now attempted to also discover the sources of fever-heat. The fever with the high pulse frequency was always looked upon as the most important symptom in acute diseases, so in pneumonia, after venesection had been replaced, other drugs and medicines were looked for to diminish the fever; for this purpose digitalis appeared to be most suitable as it diminished the pulse frequency and brought down the fever of the body and in a certain sense was regarded as a heart tonic. But the views changed, the dangers which were brought about by large doses of digitalis were soon recognized.

The condition was more evident with another remedy, veratrum, which appeared upon the scene about 1864-65 (from Würzburg). The action, even of small doses of this remedy, was remarkable; in from four to six hours the temperature fell from 104° F. to 97.7° F. and 95° F., and the pulse, from 120 to 80, 60, 40, etc., but the afebrile patients usually found themselves in such a weak and threatening condition that the physician was happy if they withstood the action of the remedy. Veratrum was soon given up in the treatment of pneumonia. Quinin took its place, the action of which was more familiar to physicians. In doses of from 1 to 2 to 5 grams it brought down the temperature (not as speedily as did veratrum); however, the patient still suffered greatly from severe tinnitus aurium, but there was no actual danger. Smaller doses, 1 to 2 grams a day were employed, without having a marked effect upon the fever, but still lowering the temperature to a slight extent without causing danger to the patient.

After digitalis and veratrum, and simultaneously with quinin, the water treatment of fever became prominent. Previously developed in England and Germany, and even used by Schönlein in enteric fever, it was prominently

brought forward by Brand (Stettin) and by a number of very eminent clinicians (Liebermeister, Jürgensen, Ziemssen, and others). Repeated cold baths were also greatly employed in the treatment of pneumonia. The cold-water treatment did not obtain the same recognition in pneumonia that it did in enteric fever, although even to-day its use is still justified, however, a milder form of hydropathic enveloping, or packs as it is called to-day, was employed, which at this time is very much in vogue.

I must now add that the inconsiderate combating of the fever is no longer looked upon as the first indication, that to the cold-water treatment another animating, strengthening action and an increase of pathological excretion is ascribed. The view expressed in antiquity was again taken up among many of the later medical authorities (Sydenham, etc.) that the fever was an expression of the natural curative endeavors, that it was well to moderate it but not to forcibly suppress it.

To this somewhat milder form of antipyretic treatment belong the modern fever remedies, the derivatives of quinin produced in the laboratory, first salicylic acid (Kolbe), antipyrin, produced by Knorr, tested by Filehne at the bedside and found valuable, antifebrin, phenacetin, etc. The last period in the revolution of the treatment of pneumonia is due to the fortunate development of bacteriology.

After the earlier investigations and endeavors in attaining the desired results of an infallible therapy of pneumonia were unsuccessful, it was hoped to reach the pathogenic agent of pneumonia with better results and to attack and destroy it. This object has shown itself to be anything but easy, and even upon this road mistakes and errors have arisen. This period is not yet closed and we may hope here to attain results which may be placed side by side with the results of sero-therapy in other realms of medicine.

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I shall now outline the therapy as practiced to-day and describe separately the individual parts of the complete treatment, viz.:

1. Prophylaxis.
2. Specific (etiologic) treatment.
3. Treatment of the fever.
4. Drug therapy.
5. Physical curative methods.
6. Dietetic therapy and nursing.

In connection herewith, I shall attempt in conclusion to develop the entire plan of treatment as far as possible, in which the treatment of the individual stages of the disease will be separated, giving especial attention also to the treatment of the epicritical stage and to convalescence.

1. PROPHYLAXIS IN PNEUMONIA

This consists in the following:

1. The prevention of contagion from pneumonia patients, particularly during periods of epidemics, or in a massed appearance or in influenza.
2. Careful (not timid) treatment of every bronchial catarrh, particularly

in the winter, in which pneumonias are more frequent, and at the time of influenza epidemics.

3. Rest and care after contusions of the thorax.

4. Even in the course of the affection which has already appeared, prophylaxis may still be considered; the prevention of damage and carelessness belongs to the therapy.

5. At this point I should like in conclusion to mention something, which does not actually belong to prophylaxis but which still requires recognition here, in so far as in the person who has already been attacked it will prevent an increase of the difficulty in the course of the disease: that is, the transportation of the person ill of pneumonia.

Dr. Hampeln of Riga read a paper before the Congress for Internal Medicine, in 1901, in Berlin. Hampeln determined that nearly a quarter of the deaths from pneumonia in the hospital at Riga occur upon the first day after the patient's admission to the hospital, nearly one-half upon the first and second days inclusive; the cause of this in his opinion, is the transportation of the sick from the house to the hospital, which is apparently not well borne by the pneumonia patient. Hampeln insists upon a rational method and proper hygiene in the transportation of the sick. The patient must not be placed in a sitting posture but should lie upon his back, he should not be dressed, only carefully covered; and during transportation he must be properly nursed. If dulness of larger pulmonary areas is already present and particularly if it is near the time of the crisis, transportation is contra-indicated.

This view of Hampeln's I believe to be justified and necessary, and I am able to confirm Hampeln's remarks from my own experience. In this connection I may emphasize that also in Germany views have been expressed which have already partly been carried out. Here in Berlin, Dr. George Meyer has been successful in improving the methods for the transportation of the sick.

2. SPECIFIC AND ETIOLOGIC THERAPY

(a) *Specific Treatment. Aborting Pneumonia*

We do not possess a true specific for pneumonia, i. e., a remedy which lessens or shortens the local pathological process in an evident manner or even cures it at once.

The earlier therapy believed that it possessed such specifics primarily in *venesection*, that is, in repeated venesection. Since Dietl's time, this previous, apparently unswerving, dogma has been dropped. Jürgensen says: The antifebrile action of blood withdrawal (venesection) is slight. The well-known English physician, Pye-Smith speaks in the same sense. Marked venesection does not shorten the course of pneumonia, it weakens the patient and protracts the process. On the other hand, Pye-Smith does not appear to be opposed to the use of slight blood-letting, particularly at the onset of the disease. Since venesection at first gradually disappeared from the therapy of pneumonia, it has lately been frequently employed, occasionally with excellent results. Several authors, particularly Eichhorst, favored this treatment. This, however, can only be understood in that in certain conditions

(cyanosis, pulmonary edema, plethora) the condition of the patient is improved and he is saved by venesection. On the other hand, the formerly widely distributed view that we were able to cure pneumonia by venesection, i. e., of shortening its course (aborting it), must be distinctly rejected: Venesection has no influence upon the pneumonic process itself. It was attempted lately to attribute a favorable action to it, in that with the blood obtained by venesection a certain amount of toxins were eliminated from the body, that is, from the lungs. For the time being, such an idea is entirely a supposition, we would first have to prove how much toxin is contained in the blood, and whether by means of venesection more than a quantité négligeable is removed, without an immediate re-formation of them occurring.

The belief that pneumonia could be aborted by venesection, maintained itself for quite a long time. As a young military physician, in 1856, I still saw such an experiment. During military maneuvers a soldier was taken ill with a chill and a hemorrhagic expectoration; a colleague employed venesection; on the next day the patient was well and remained so. My colleague maintained that he had aborted pneumonia. In fact, such cases are very persuasive, but also very delusive. The process was not proven with certainty; besides there are pneumonias which last one day, which run their course in from twenty-four to thirty-six hours without any form of treatment. The conditions are about the same as in the case of venesection upon the sixth day of the disease, by which means Schönlein believed he had brought about the crisis. The probability that the marked action brought about by venesection would have occurred in the natural course of events is at least very great.

Ancient medicine possessed more auxiliary remedies which were looked upon as specifics in pneumonia; I have already previously mentioned antimony and also calomel. At the beginning of the nineteenth century, mercury (particularly in England) was employed in all inflammations ("antiplastic curative effect"); it was also maintained that it was able to resolve pneumonia. Mercury in the form of calomel or corrosive sublimate even played a part later on, for in the beginning of bacteriology it was again brought forward as the most powerful antibacterial remedy to destroy the pathogenic bacteria in the body; however, these attempts were soon abandoned.

Lead acetate, which for a time was looked upon as a specific for pneumonia, has been given up entirely.

In a certain sense, also *digitalis*, quinin and hydrotherapy were looked upon as specific curative methods. After these remedies were as good as forgotten for many years they were again brought forward and advised from this and that quarter as especially active curative measures. The treatment of pneumonia with large doses of *digitalis* has lately been advised by Dr. Petrescu (Bucharest); also A. Fränkel has expressed himself in a similar manner. By others the treatment by quinin has been praised, as well as the treatment of pneumonia by hydrotherapy, which has gained new adherents. We gladly admit that all three of these remedies used with caution at the right moment will help the patient and improve his condition, but I must protest against designating them as specifics, as well as against the presumption that a consequent exclusive treatment by one of these remedies is preferable to the use of other medicaments.

(b) *Etiologic Therapy. Serum Therapy*

By etiologic therapy, we understand those measures which directly or indirectly attack the infectious agent (known or unknown) and diminish or destroy the pathogenic agent or its action and thus remove the disease. To the most brilliant triumphs of this art of therapy belong Pasteur's hydrophobia inoculation and the treatment with curative serum of diphtheria and tetanus discovered by Behring. To this may be added the streptococcic curative serum of Marmorek, and, so far as I am informed, also the pest serum of Yersin. For pneumonia also such investigations have been instituted but up till now without a decisive result.

Before entering upon this subject, I will report the first endeavors regarding etiologic therapy, for although they have remained without results, the authors in question, the brave pickets in this realm, deserve all honor and should not be entirely forgotten.

The first trials belonging to this endeavor were made with carbolic acid and mercury, both tested in the early period of bacteriology and found to be mighty opponents of bacteria, capable of destroying them or of rendering their development impossible. However, both were without action on the infected organism.

As far as I know Lépine¹ was the first to make a trial with antiseptic injections into the parenchyma of the lungs, of a solution of corrosive sublimate of 1 to 4,000, of which solution he injected a few cubic centimetres, but without result. The same negative results he obtained with a tincture of iodine and with sodium benzoate in the pneumonic area. Inhalations of antiseptic substances were also without result.

Of greater importance were the attempts with sero-therapy, at first with artificial serum. Thus, I intend to designate the trials with subcutaneous or intravenous normal salt infusions. About $\frac{1}{2}$ litre was injected, following a previous venesection.² This physiologic salt infusion was very much in vogue in France for some time and thence found its way into neighboring countries, for example, Austria. Finally, sterilized sea-water was taken, the composition of which was looked upon as particularly adequate to human serum. In my clinic I have also used such physiologic salt infusion in various infectious diseases, also in several cases of pneumonia. I have also injected sugar (fruit sugar), $\frac{1}{2}$ per cent. solution plus $\frac{1}{2}$ per cent. salt solution, and also a 1 per cent. sugar solution alone, these being used subcutaneously, and in rare cases intravenously. The sugar was supposed to act partly as an anti-parasite, partly as a nutritive substance, particularly to the heart. I have seen very encouraging results, particularly in puerperal fever and in pneumonia. I have also even lately employed this method and do not think of abandoning it until something better is at hand. The subcutaneous infusion is unquestionably quite harmless. Naturally, I cannot claim remarkable

¹ Sur le traitement local de la Pneumonie fibrineuse par les injections intraparenchymateuses. *Compte rend.* 1885.

² Dr. Paesler (Leipsic) says: Normal salt infusion produces a rise in fallen blood pressure.

results. In spite of this, however, I believe that this method deserves further consideration than has been given to it in Germany thus far.

A very optimistic description is given by Dr. Reynand (Marseilles) [*La Saignée et la transfusion saline hypodermique dans les maladies toxiques et infectieuses*, Arch. génér. de Méd., 1900]. Regarding his experiences during three years, in the Hôtel Dieu de Marseille, he reports that he employed salt infusion in all cases of auto-intoxications, in intoxications in infectious diseases and praises the results; especially 77 cases of pneumonia were treated in this manner. In 20 cases death occurred, in 30 surprisingly rapid recovery took place. This result cannot be looked upon as absolutely convincing.

A third method consisted in introducing irritating substances, and such as would produce inflammation (oil of turpentine and the like, by subcutaneous injection) so as to produce at the point of injection a profuse accumulation of leukocytes (hyperleukocytosis) called by the French *Abcès de fixation*.¹ I was among the first to make these experiments. They start from a proper idea, worthy of note, namely, this, that a profuse leukocytosis has an antiparasitic action. Lately Buchner has concluded from his investigations that the leukocytes prepare alexins, that is, immune bodies. Several years ago in puerperal fever and in pneumonia I used this method quite frequently, at first with encouraging results. When I then employed the method in a case of malignant endocarditis there was absolutely no result and I did not return to its use.²

Actual serum therapy in pneumonia, according to the example of Behring, attempts to produce a curative serum which will neutralize the toxins of the pathogenic agent and finally neutralize the diseased organism. Such endeavors have been attempted for years in pneumonia and although up till now no satisfactory results have been obtained we are, nevertheless, justified in hoping that in a not too distant future the desired goal will be reached. Up till this time but few endeavors have been made in this direction in Germany.

The first experiments of this kind in my clinic were made by G. and F. Klemperer in the year 1892, and in the same year were communicated to the Congress for Internal Medicine in Leipsic. These consisted in injections of curative serum taken from rabbits which were immunized by cultures of pneumococci. In the 12 cases reported by Klemperer in Leipsic the injection of serum was constantly accompanied by a fall in temperature, with such regularity that accidental conditions could be excluded; with a fall in temperature almost always the pulse declined, not so frequently the respiration; the local process in the lungs was not influenced by the injection. Only in 5 of the 12 cases did the fall in temperature coincide with the regular crisis; in the other 7 cases, after some hours (usually from six to ten) a new rise in temperature occurred, which could only be temporarily lowered by a renewed injection of serum. The brothers Klemperer concluded that these results were unmistakably a curative action of the serum; however, the toxin-

¹ *Foucher*, *Thérapeutique des infections pyogènes généralisées*. Lyon Méd., 1891.

² The remedies which produce general leukocytosis, or even hyperleukocytosis, such as pilocarpin, thymus substance, etc., must also be thought of in this connection. They have all been used in a similar sense but all without success (compare Korányi's report).

binding effect was very transitory and too slight, as the animal from which the serum was obtained could only be forced to a relatively slight degree of immunity.

The results were encouraging, but not decisive. They were kindly accepted (Lichtheim) and the trials were repeated in various quarters, usually with a good, even though not with an absolutely convincing effect.

A second series of experiments consisted in the attempt to obtain the serum from the blood of convalescents from pneumonia (and also after other infectious diseases) and this was injected in other pneumonia patients at the height of the disease. Such trials were made in my clinic by Huber and Blumenthal. Before they were published¹ Dr. Weissbecker² published similar trials, and as he believed with very remarkable results. This was perhaps claiming too much, but, nevertheless, they were remarkably conspicuous and encouraging. The continuation of these trials was frustrated by the difficulty of obtaining sufficient blood serum from convalescents and to save it until needed without influencing its activity.

A third series of experiments was made in the same direction taken by G. and F. Klemperer; only in the preparation of the serum, instead of small animals, such as rabbits and dogs, larger animals (goats, horses, asses) were employed, and it was hoped by utilizing these animals to obtain a high-graded immune serum and in much larger amounts.

In this manner Dr. Pane (Italy) produced an antipneumonia serum which he reported in the *Riforma med.*, October, 1898. By subcutaneous injections of virulent pneumonia in horses and in cows he obtained an antitoxic serum, which was much stronger than that obtained until now from rabbits, and which in animal experiments was protective against a twenty times lethal dose of pneumococci culture. Utilized in 10 cases of severe pneumonia (in doses of 20 cc. daily), this serum in 7 patients after the second injection produced a rapid and complete recovery. The 3 other patients died in spite of the same treatment, however, all 3 were alcoholics and 1 of these patients was well advanced in age, and suffering from nephritis at the same time.

These reports of Dr. Pane which were supported by Foa, Maragliano and others,³ have been only partially confirmed from other quarters.

Dr. Schonig, in Kingston, in the *British Medical Journal*, 1899, reported his results with Pane's antipneumonia serum and came to the following conclusions:

1. In doses of 1 cc. in rats the serum has a decided protective power against 4 to 5 cc. pneumococci culture.
2. It does not possess any protective power against a typical coccus obtained from a lethal case of pneumonia.
3. There are varieties of the pneumococcus⁴ which until now could only be differentiated by their action upon pneumonia serum.

¹ Berliner klin. Wochenschr., 1897, xxxi.

² Zeitschr. f. klin. Med., 1896, xxx; 1897, xxxii.

³ Italien. Congr. f. innere Med. Münchener med. Wochenschr., 1897.

⁴ Dr. Huber (in my clinic) observed that pneumococci cultures prepared in the dry hot summer of 1901, in which almost no pneumonia occurred, possessed but very slight virulence; even after transplanting once they would no longer grow in the culture media.

Other reports were communicated by Antonio Fanoni.¹ He reports 6 cases of pneumonia which were treated with Pane's antipneumonia serum. The results surprised Fanoni. The injections were given twice daily (about eight o'clock in the morning, and nine o'clock in the evening (each injection of 10 cc., by means of a Pravaz syringe, into the posterior axillary line). These were continued as long as the temperature rose above 104° F. No other medication was used except hygienic measures. The diet: 1 to 1½ litre of milk, some bread, yolk of an egg, alcohol with water. In all 6 cases the result was surprisingly good. Fanoni's conclusions are as follows:

1. Pane's antipneumonia serum is the rational curative agent of pneumonia (about the same as Behring's serum in diphtheria).
2. The injection is painless, without local reaction.
3. A serum more than five months old no longer possesses activity.
4. In all cases a good effect and rapid improvement was determined from the serum injection (increased rapidity of resolution).

From other sources no complete reports regarding the importance of Pane's pneumonia serum have appeared. In my clinic for some time analogous labors have been instituted. As we have not been able to obtain explicit reports regarding the method in which Pane obtains his serum, we cannot know whether we are proceeding along the same lines or not. These labors have not yet been concluded.

3. THE TREATMENT OF THE FEVER

In pneumonia the severity of the febrile symptoms which dominate the entire course of the disease, has required that, from antiquity up to the latest time, the first indication of treatment should consist in combating the fever. The old therapy of venesection, of cool drinks, of withholding nourishment, etc., were directed against the fever. Later, luke-warm and cool fomentations, and warm and hot steam for inhalation were added.

The diaphoretic method played a great rôle. The patients were packed in their beds, received warm drinks and diaphoretic remedies (lemonade, and vinegar lemonade, ammonia preparations); wine of antimony also has a diaphoretic action and lowers temperature. The use of pilocarpin lately was but transitory. The diaphoretic method was employed to artificially produce crisis and to remove the fever. This method was retained for quite a long time in mild fevers due to refrigeration and the like, and even to-day, especially in the realm of popular medicine, is quite in fashion. In severe diseases, as pneumonia and enteric fever, it has always shown itself to be ineffective, and it even raises the temperature and increases the symptoms dependent upon the temperature (extreme congestion, unrest) to a marked degree. It has, therefore, been abandoned and we limit ourselves to-day to carefully observing perspiration in the fever patient, particularly at the time of crisis, and in general we fear displacing this condition by the application of cold.

¹ Of the serum, Fanoni used two concentrations: No. 1, mild serum, No. 2, strong serum; the former was used in mild cases of pneumonia, eventually at the onset of the disease; the latter was reserved for severe cases and in these severe cases the dose was doubled and tripled.

The cooling treatment of the fever was employed in the form of cold applications, cool baths. With the onset of hydrotherapy, the cold-water treatment of the fever in pneumonia was developed, as well as in enteric fever, and other infectious diseases. In Schönlein's clinic, an ice-bag upon the head was almost always employed and cool drinks and cold applications upon the chest were not feared.

In the sixth decade of the previous century, the treatment by repeated cold baths was also employed in pneumonia, but has not shown itself to be as useful as in enteric fever. The greatest majority of clinicians decline employing them; I only prescribe them for distinct indications, in high fever, excitement without marked dyspnea, and with a strong pulse.

Instead of this method of therapy by baths, modern treatment has gained greatly by cold applications, by enveloping the patient in coils, which is found to have been useful in practice, in children as well as in adults.

Antifebrile remedies begin with quinin on account of its remarkable action in malaria, then follow digitalis, veratrum and, finally, besides quinin, the newer antipyretics, the use of which to a moderate degree is almost general and by no means unjustified.

However, a decided transformation has occurred to-day regarding the indication for antifebrile treatment in general. Since the bacteriologic era, the views regarding fever have changed. It is no longer the cardinal symptom of the affection, but the effect of the development of bacteria.

Whereas the earlier medicine regarded the treatment of the fever as the first indication, the question has arisen to-day and is much discussed: Should we and dare we treat the fever? This question for the present art of therapy, in febrile diseases, and also in pneumonia, is of great interest, so that two prominent investigators, Prof. Stokvis (Amsterdam) and Prof. Lépine (Lyons),¹ were asked at the International Congress in Paris to report regarding this question. I cannot enter into the details regarding this report, but both investigators unanimously arrived at the decision that the fever is to be looked upon as a curative endeavor of nature, which protects the sick organism against the bacterial power of the toxins and favors the production of antibodies. Professional experience has decided in a similar sense, in some instances the physician wishes a good marked fever, because experience has taught him that such cases run a more favorable course than those in which there is a feeble febrile reaction. These are the weak cases, the asthenic pneumonias, which in the main present a more unfavorable prognosis than the sthenic synochial form.

Former endeavors to forcibly suppress the fever by large doses of antipyretic remedies, we cannot favor; on the other hand, a mild use of these remedies is often beneficial in reducing the temperature somewhat, allaying irritation and unrest, and thereby quieting the patient similarly to the action of narcotics. Antipyretics render the condition more mild and favor the occurrence of convalescence; but all of them have an action upon the heart and must be used with caution. This is true of quinin, which recently has

¹ *Lépine* (Lyon) und *Stokvis* (Amsterdam), *Doit-on combattre la fièvre?* Paris, 1900, xiii. Congrès internat., Paris, 1901. O. Doin.

been urgently advised by Aufrecht in the therapy of pneumonia, in an analogous manner to that of all the newer remedies. Antipyretic treatment is not schematic, but is to be used in each particular case according to individual circumstances.

4. DRUG THERAPY

As has been repeatedly remarked, we do not possess a specific remedy which has a pathological action upon the pathogenic agent of pneumonia; from this, however, it does not follow that drug therapy is superfluous or that it can be dispensed with. I should like to say the less certain and schematic the therapy of pneumonia is, the more carefully and cautiously must the remedies be chosen and employed which are active in moderating threatening symptoms, in ameliorating the distress, and raising the strength of the patient. Without doubt, we may treat a pneumonia of mild grade without any drugs, but even in such instances the case will be milder if suitable remedies are administered to the patient; whether the patient has faith or not, the regular administration of a medicine gives him the comforting assurance that his disease is carefully watched over and methodically treated.¹ From this it does not follow that medicines are to be continuously administered. Pauses may be made, but always according to the individual requirements of the patient. Only the fanatics of a drugless therapy absolutely abominate every drug—habeant sibi.

1. Among such indifferent remedies I class the former tisanes, solut. gummos., decoct. alb. (Sydenham), potio rivieri. I prefer small doses of antipyretic remedies (sodium salicylate, sodium benzoate or aspirin, pyramidon, 1–2–3 grams per day in solution); I have in view the object of seeing how the patient bears such remedies, which later, perhaps, may become necessary in larger doses.

2. In place of indifferent remedies, I prefer those which have been accredited and in use for a long time. Historical authority, occasionally in both physicians and laymen, produces great confidence in them, which makes them useful and desirable.

Among these I count the old specifics, saltpeter (wine of antimony), potassium and sodium nitrate; these at the present time are entirely obsolete, others have been substituted; I am partial to sodium benzoate in solution. Lately creosote and creosotal have been advised (creosotali 10.0, emulsion 60, teaspoonful four times daily). A commercial genius has rebaptized them into pneumoform or pulmonin, and perhaps he is doing a good business with them.

3. The antipyretics are of great importance: their indication in general has already been discussed. We must here mention the individual drugs. In importance and dose they are nearly equal. Some have been discontinued on account of disagreeable after-effects, thus, antipyrin, the first antifebrile remedy which was chemically produced, on account of its unpleasant subsequent

¹ Sir William Broadbent (Practitioner, March, 1900) says quite properly: "In a great number of cases it cannot be maintained that a regular use of medicines of any kind is necessary, but, as a rule, it is a comfort for the patient and his friends when they have the feeling that something is being done for the patient."

effects is less in use. Phenacetin acts less upon the temperature, having rather a quieting and anodyne effect; in larger doses and after prolonged use, it readily produces cardiac difficulty. Salipyrin, praised as a specific for influenza (*cui bono?*), has also been found useful in pneumonia. The drugs both in use and most serviceable at present are sodium salicylate, pyramidon and aspirin. With any one of them, we begin with a dose of $7\frac{1}{2}$ grains, one, two to three times daily, and observe how the patient bears this before proceeding to larger doses. The mildest remedy of this kind is sodium benzoate. Finally, quinin must not be forgotten, this is well borne and in ordinary doses has no ill subsequent effects and with physicians and laymen it still retains historic authority. That it possesses an especially active influence upon pneumonia may be true in this or that case, but I cannot recognize this as a general rule; neither can I admit a particular difference between internal and subcutaneous administration. In the latter case the effect occurs more rapidly and the stomach is spared, but subcutaneous injection sometimes is quite painful.

These drugs in the course of pneumonia are used quite properly, freely and frequently. They are capable of reducing the temperature somewhat, and, simultaneously, have a quieting and anodyne effect. They are, therefore, particularly applicable at night before the evening meal, and with relative ease bring on a quiet night and a morning remission of the fever, which acts beneficially, and encourages physician, patient and friends. The combination of these remedies with opium or morphia in the evening (sometimes also during the day) is very serviceable, and I can confirm the observation of Dr. Paffrath without especially recognizing therein a "specific curative method."

4. To these may be added morphia and other hypnotics. In the beginning of this discourse I have already mentioned the careful but simultaneously salutary and almost indispensable use of the great remedial agent in the course of pneumonia. I begin with 0.005 gram, injected subcutaneously in the course of the day, to observe the first action and to note how the remedy is borne. In very high fevers, during the evening exacerbation, it is often badly borne, then it is all the more unnecessary as the patient appears to be somnolent and does not complain. It is indispensable in restless insomnia (versatile form) and in the delirium before and after the crisis. It is especially useful after the crisis if sleep does not occur. During the first days of pneumonia it is well borne and increases the rest at night. It is contraindicated in cyanosis and in marked dyspnea (occasionally, however, small doses are risked in great restlessness of the patient or with a very weak, small pulse). If accidentally the dose given acts powerfully, and sleep, therefore, is heavy and deep, the respiration disturbed, the patient should not be allowed to sleep too long, he should be awakened after one or two hours, and some coffee given to him until sleep becomes quiet and uniform. Sleep must be carefully watched for it may happen that the patient does not awaken and death occurs. I previously described such a critical condition, which fortunately terminated favorably.

Dover powder must be mentioned, which has been a favorite remedy for some time. Ten grams contain 1 gram of opium, 0.1 to 0.2 per dose is administered.

What has been said of morphia is *ceteris paribus* true of other hypnotics, morphia is the most useful, subcutaneously administered it acts rapidly and the effect passes off relatively soon, i. e., an undesirable subsequent effect need scarcely be feared. For patients that dread opium or morphia, we now have a number of remedies which are less known to the laity: Heroin, dionin, codein, peronin, which may be employed subcutaneously as well as internally. The combination of these with bromide salts and with antipyretics at the right moment is very serviceable.

In the main, the physician must act according to his judgment and according to experience, always remembering his great responsibilities. He is not to neglect the opportunity and the possibility of useful medication, but he is also to carefully guard against the too profound action or the undesirable subsequent effects of his remedies.

5. *Expectorants, tonics.* In the further course of pneumonia, from the third to the sixth day, when the strength of the patient begins to lessen, tonics are in place. I prefer the exhilarating expectorants, the preparations of ammonia (liquor ammonii acetatis, ammonium muriate), apomorphin, potassium iodid; further, senega, benzoin, camphor, menthol emulsion, terpin-hydrate; however, other popular expectorants may also be used.

Stimulants simultaneously act as tonics, such as the so-called quinin decoction (emulsio chinata, Schönlein) with muriatic acid or liquor ammonia, etc. Iron is also used as a tonic. Thus, one of the most prominent physicians of England (Sir Andrew Clark) advises in a very rapidly developing pneumonia the perchlorate of iron. Also in our clinics and in practice, liquor ferri acetatis and the muriate of iron and ammonia were now and then in use, at present they have been generally abandoned. Nevertheless, some physicians and patients still have confidence in these remedies.

Important and necessary tonics, simultaneously heart tonics, are the various forms of alcohol: wine, brandy, wine of quinin, cola wine. Germain Sée and Jürgensen (*Croupous Pneumonia*, 1883) were warm adherents of the alcohol therapy (1 litre of wine) advised by Todd. *Ne quid nimis*, may be said here. But we should not fall into the opposite error of the adherents of temperance. Alcohol and wine are necessary, in my opinion, to refresh the patient, for the occasional stimulation of cardiac action and even of respiration, thus during the collapse of crisis. These remedies are indispensable in alcoholics. Why should a remedy which is so useful to the patient be withheld from him only perhaps because others drink too much? Later on, in discussing the nutrition of the pneumonic, I shall return to the alcohol question (page 598).

In addition to alcohol, coffee, tea (caffein), and especial heart tonics, digitalis, strophanthus, adonis vernalis and convallarium may be added. Regarding the indications for the use of digitalis, these have already been explicitly discussed; I absolutely reject strong doses, also I do not recognize a treatment of pneumonia based upon digitalis alone. The use of this remedy should only be for general indications. When the pulse before or after crisis begins to become weak the use of digitalis is justified. I favor small

doses of the infusion (0.6 ad 150 for two days), or also pulvis digitalis with caffein,

R Pulv. Digit.	0.005–0.01
Caffein. citr.	0.05
Sacch. lact.	0.25

M. Sig., two to three times daily.

Or, instead of caffein, camphor or also flores benzoës in the same dose (I rarely give more than a total dose of 1.0 digitalis).

As heart tonics, there should be further mentioned cola (tincture of cola, cola wine) and nux vomica (tincture nucis vomica, or strychnia in powders, pills, alone, or with other drugs). Liebreich advises subcutaneous injections of nitrate of strychnia (2 to 4 milligrams once or twice a day in cardiac weakness. In other countries (America, Russia) this manner of using strychnia for similar indications is quite common. I can report very favorable actions regarding this remedy.

6. To these internal remedies, external applications must also be added; to-day of no great importance, nevertheless in the individual case of use are: Mustard plaster, blisters (applied for a short time), friction with aromatic spirits, turpentine, creosotal or camphor vasogen, etc.

7. *Inhalations* of warm water (Ems water or salt, menthol, etc.) are not infrequently grateful to the patient. Formalin is usually too irritating. Of greatest importance is the *inhalation of oxygen* which lately has obtained more recognition and use.¹ Naturally, only an amelioration of the condition of the patient can be expected, in particular in regard to dyspnea. Whoever looks upon this as a specific treatment of pneumonia will naturally be disappointed. With well developed cyanosis in pneumonia (with pulmonary edema) the remedy is mostly used too late. In the intermediate stages these inhalations frequently relieve the respiratory difficulty (air-hunger) of the patient and at the same time stimulate respiration. I cannot enter into more details at this point.

5. PHYSICAL TREATMENT: HYDROTHERAPY AND MASSAGE

Hydrotherapy or water-treatment, as is well known, is as old as medicine itself. Hippocrates practised it, Asclepiades earned the name of Psychroloutes (cold-water bather). The Roman physician, Antonius Musa, earned great renown by his fortunate water cures with the Emperor Augustus and the poet Horace. In the middle ages hydrotherapy had been forgotten, but was again introduced into clinical medicine by Currie (1792) in England, and by the brothers Hahn, in Germany, etc. Schönlein in his clinic made most thorough use of this treatment. The labors of the layman, Priessnitz, were primarily responsible for bringing the water treatment again into prominence.

Hydrotherapy may be divided into the use of warm and of cold water. In former times (Sydenham and later) the preference was given to warm water in the form of warm fomentations, warm inhalations, warm tisanes and also

¹ Compare *M. Michaelis*, Zeitschr. f. diätet. u. physikal. Therapie, iv, 2; v. *Leyden*, Festschrift für Jaffé, 1901.

warm baths, for the most part with the object of producing perspiration, and, with this, the cessation of the fever.

At the present the cold-water treatment is prominent and is preferred, partly for cooling, partly for refreshing and strengthening. The treatment of fever by cold-water baths, already practised in England by Currie, was first introduced into Germany by Th. Brand of Stettin (1861) as his own method. Brand administered baths of from 15° C. to 20° C., the water only being one hand high in the tub, the patient placed in the water and cold water several times thrown over him. This treatment was shown, especially in the strictest form, as was required by Brand, to be too hard for the patient. In the moderated form of luke-warm baths which could be cooled by the addition of cold water to the bath, from about 25°–20°–18° C., to which might be added cold affusions, packs and the like, this method being warmly advocated by Liebermeister, Jürgensen, Ziemssen and others. In enteric fever, treatment by baths has been generally adopted; in pneumonia repeated cold baths have not obtained general recognition, although in individual cases unquestionably they have been utilized to good advantage.

In the journal edited by Prof. Winternitz (*Journal of Clinical Hydrotherapy*), a number of papers upon the application of water in pneumonia have been published, which show the present stand of the case, from which we shall borrow the most important points. These frequently permit the recognition of coquetry with so-called "nature-healing science." Among them the paper of Dr. A. Pick: *The Hydriatic Treatment of Pneumonia*, 1900, Nos. 7 and 8, is the most remarkable as this author is very near to Prof. Winternitz: The hydriatic treatment of pneumonia consists of the application of cool baths and partial washings, as well as of the application of cold to the small of the back. The baths should have a temperature of from 12° C. to 24° C., they are to be watched over by the physician, and the patient is rubbed simultaneously by three persons. Duration of the baths eight to ten minutes. Frequent cold douches to the nape of the neck. The thermic effect of these baths is slight, the chief effect consists in a conspicuous improvement of tension in the pulse, a reduction in the number of pulse beats, combined with an amelioration of the general condition and a clearing of the sensorium.

It will be noted that the use of the baths presupposes a trained person who understands the necessary care, so that they cannot be used in every hospital, much less be carried out in private practice.

In private practice and in the clinic, as a rule, similar procedures are used: Ice-bag to the head or cardiac region, packs about the chest or the abdomen, which, however, must be so loosely applied that they do not disturb respiration and do not press upon the patient.

Partial cooling of the body by towels which are dipped in cold water has been advised, however, they are not pleasant and refreshing to all patients; some patients wish to be undisturbed, and are opposed to these many procedures. Exclusive treatment with partial baths, that is, Priessnitz compresses, is advised by Dr. Pick for severe cases with markedly distributed hepatisation or high-graded dyspnea, as well as cardiac asthenia with small intermittent pulse. In delirium, cold compresses are to be applied to the head.

Another author, Simon Baruch, New York (Hydrotherapy of Pneumonia), says: Hydrotherapy is by no means a specific remedy in pneumonia, its proper application, however, brings about amelioration and unquestionably diminishes the mortality. The indications are: 1, to strengthen the nervous system; 2, to strengthen the heart; 3, the elimination of deleterious pathologic products (toxins); 4, to ease the condition of the patient. The author does not so much advise cold baths as the application of cold compresses. We may coincide with this and only hope that these measures may offer to our pneumonia patients all that the enthusiastic author promises.

By clinicians in general, the usefulness of cold water treatment is now commonly recognized. Ice-bags to the head and to the cardiac region, ice-cold compresses, cold packs upon the chest and upon the abdomen, eventually cold partial washings, may certainly be looked upon as useful and grateful in the treatment of pneumonia. But the individuality of the patient must always be considered in such instances.

I will only add what the well-known and prominent English physician Pye-Smith says in regard to this point: Ice-bags upon the abdomen produce a lessening of the blood temperature and an increase of general blood tension (action upon splanchnic), finally, improvement in the pulse frequency, greater depth of respiration. Other physicians have confirmed these favorable effects. Elderly persons, or fat or weak patients, do not bear the ice-bag well, in these cases cool compresses are to be used. Among German clinicians Jürgensen, Bäumlér, Nothnagel, and others, have expressed themselves favorably regarding the application of hydropathic procedures, as well as Korányi in Budapest. From many sides it is emphasized that hydrotherapy, the timely administration of alcohol (brandy and the like) cannot be dispensed with in combating the cardiac asthenia.

In connection with hydrotherapy, I shall mention the manual treatment (massage) which very frequently is combined with the former. Dr. Ingesco Müller¹ says that this has been practised in Sweden for years and been found very useful. The stitches in the side which hinder respiration are to be first alleviated. For this purpose (besides medication and packs) intercostal friction is to be used, which in most cases acts rapidly and with certainty. The physician by means of palpation finds the painful area upon the affected side; here with the tips of the fingers of one hand he employs energetic friction but of limited extent, whereas with the other hand the same manipulation upon the corresponding area of the other side is carried out. It is known that the sensitiveness of a mechanically irritated nerve with simultaneous irritation of another may readily be removed. At first during this massage the patient holds his breath. If, however, the physician persists, the patient finally must inspire deeply; this quiets the patient and renders the painful area less sensitive. Tapping the side lightly with the hand, as well as massage of the cardiac region are said to be excellent methods of stimulating the heart, making the pulse fuller and quieter. By mild *vibration* the resolution of pneumonia is favored, besides friction is advised for headache and abdominal pain.

¹ Deutsche med. Wochenschr., 1900, lii.

6. DIETETIC TREATMENT (NUTRITIVE THERAPY) AND NURSING—PLAN OF TREATMENT

The diet (nutrition) in pneumonics *ceteris paribus* is to follow the same principles as in other febrile diseases. Although dietetics, even in the most ancient times of medicine, had been cultivated and appreciated, only in the last decades, however, has it risen to the dignity of a scientific principle, and become an integral part of medical treatment.

The physicians of antiquity had distinct rules regarding the diet of febrile patients and partly very rigorous ones. In the first days of the illness no food was given and some physicians even prohibited fluid, on the other hand the vessels (intestines) were to be evacuated. Nutrition primarily consisted of tisanes and thin flour soups, in a long duration of the illness thicker flour soups, chickens and wine were administered. There was no thought of a scientific conception of diet in disease, for the most simple knowledge regarding metabolism and digestive processes had not as yet been attained.

During the middle ages, particularly the school of Salerno,¹ was distinguished on account of its dietetic measures; pneumonia was principally treated according to dietetic rules.

During Holland's pre-eminence the clinical school of Leyden was superior to all others. Boerhaave, the greatest medical authority of the same, also gave dietetic rules for pneumonia, which could be referred to Hippocratic principles: Semiliquid diet, consisting of anti-inflammatory (anti-heat producing) substances. Somewhat later Reil taught in Germany: in fever, oil ($\frac{1}{2}$ litre several times a day), milk, spermaceti with sugar are to be given.

Wunderlich still more exhaustively describes the diet and nursing of the pneumonic. He prescribes the following general régime: The sick-room should be of a uniform temperature, not too warm (so as not to cause sweating), the air should be pure; the room should be as quiet as possible, no talking, the patient is to be covered. The temperature of the room is to be from 14° R. to 16° R.; when the fever declines, as well in children as in the aged, from 15° R. to 17° R. Chilling is to be avoided when changing the bedclothes of the patient, especially avoiding examinations while the patient is sweating. The patient may take any position in bed which is comfortable to him. During the first days the patient does not require food (*sic!*). Only with the expected crisis, from the fifth day on, a thin meat soup and diluted milk are to be given, and solid food only after defervescence. In older children and in the aged, as well as in debilitated individuals, more liberal diet may be allowed (milk, meat broths, wine). In alcoholics, alcohol should not be entirely withdrawn. When the pneumonia becomes protracted the diet is more important than drug therapy. Fluids are to be freely administered; these are to consist of glutinous sugar-containing material and to be administered

¹ Munsandinus (*De cibis et potibus febricitantium*. *Collectio Salernitana*, ii, 407) was the first to emphasize that the diet of fever patients is to be "*subtilis et tenuis*." He lays stress upon the fact that everything should be given the patient in "*vase pulchro*," then, in spite of loss of appetite, it will gladly be taken by the patient. As a cooling remedy he advises pumpkins and pickles prepared in different ways.

cool; irritating drinks are to be entirely avoided, in so far as distinct indications do not exist for their employment.

Scientific dietetics (nutritive therapy) began with the great chemist, Justus v. Liebig in Munich, who founded the physiology of nutrition in metabolism and also discovered the first artificial nutritive preparation, Liebig's beef extract, which is still well known and much employed. The original division of nutritive materials into respiratory or heat-producing products (food free from nitrogen: fats and carbohydrates) and in tissue-constructing products (albumin products) has naturally been abandoned (only among the laity, on account of its simplicity, it still has many adherents). Nevertheless, further progress in the physiology of metabolism was added to the researches of Liebig, upon which to-day the scientific therapy of nutrition rests. The names of the Munich schools: v. Pettenkofer, Bischoff, Voit, Rubner and others are honorably connected with the present teachings of metabolism in health and disease.

Primarily, naturally, the results of scientific investigations of metabolism and nutrition were without influence in the diet of fever patients. The old principle upon which all laws were based remained determining: The withdrawal of nourishment was to diminish the fever. This was carried out strictly by the physiological school in France (Broussais, Bouillaud).¹ Primarily this standpoint was not altered. For even Liebig's division of nutriment into heat and tissue-producing substances just mentioned seemed to favor the old views that fever patients rejected meat and other albumin products, on the other hand, gladly accepted flour soups and flour foods. In Schönlein's and Traube's clinics the old dietetic principles still coincided entirely with the old indications of moderating the fever by the withdrawal of nutriment. Traube would deduce that the measured temperature of the fever patient was the result of the actual fever-heat minus the heat production diminished by the withdrawal of nutrition.

The presumption that the increased heat in fever was due to raised combustion in the body was looked upon as almost self-evident and appeared to be scientifically proven when Traube and Jochmann (1853) in their celebrated work upon metabolism and fever determined an increased excretion of urea which they concluded was due to an increased decomposition of nitrogen in the body. For a complete proof naturally, the CO₂ test of the excretion was still absent, which was more difficult and which required newer methods. In his later explanations Traube, however, showed that the increased fever-heat might be due to an increased heat production (combustion in the organism), as well as to retained heat (diminished liberation), and that particularly the fever chill was connected with the latter modus. The investigations regarding CO₂ excretion in fever which now followed (Leyden,² Senator,³ Liebermeister⁴)

¹ The following sentence may be quoted from Bouillaud (Broussais' School): *Tant que dans une maladie aiguë fébrile vous n'aurez point complètement ou à peu près éteint le mouvement febril, ne prescrivez pas le plus léger ailment.*

² *Deutsches Archiv f. klin. Med.*, Bd. vi, 1869. I. Calorimetrische Messungen. II. Wägungen.

³ *Untersuchungen über den fieberhaften Process und seine Behandlung.* Berlin, 1873.

⁴ *Handbuch der Pathologie und Therapie des Fiebers.* Leipzig, 1875.

proved the diminution of CO_2 excretion, therefore a diminution of carbohydrate combustion in fever, but to a relatively slight degree; I found an increase of CO_2 excretion averaging about 20 per cent.

Senator demonstrated (in the dog) that the organism could withstand very high temperatures without utilizing more O and without excreting more CO_2 than in similar external circumstances in conditions of apyrexia.

Even by these investigations it was shown that the increased heat production in fever was not exclusively due to increased combustion of material, but that, simultaneously, a heat retention must exist which probably was of greater importance than the former. These conditions were more positively proven by my calorimetric investigations of fever patients.¹ From this very complicated process in fever a peculiar action of the fever-producing cause could be concluded, which altered the heat regulation of the body, which, as compared with the normal variation, showed the noteworthy result—naturally within wider limits than the normal—that the febrile organism also endeavored to retain a quite uniform limit of rise in temperature. Liebermeister designated this in a striking manner in that he said: “The blood temperature in fever is maintained at a higher limit than in the normal condition.”

These results of investigations were bound to shatter the old views that fever heat was principally due to increased product combustion, and, further, it had to be doubted whether increased administration of nourishment actually increased fever heat and whether a decrease diminished it. Experimental researches demonstrated the opposite. By numerous investigations at the bedside, it was proven that an increased amount of nourishment did not increase the febrile temperature. Now, however, a second condition was added to this. Besides a rise in temperature in fever, the physician was compelled to note that fever patients, even when they recovered, lost decidedly in body-weight, in some diseases so markedly that the body-fat almost disappeared (“consumption”) and that death was the result of this disappearance. This phenomenon was also referred to increased combustion: “The fever consumes.” This process was designated as febrile consumption, consumption in fever, and this was in the highest degree interesting to the physician. Here also criticism of the older views was bound to become perplexed: the slight increase of combustion in fever could hardly produce such a marked loss in body substance. The first scientific work regarding consumption, i. e., death due to inanition, is represented by the classic as well as cruel work of Chossat,² who caused animals to succumb to starvation and determined the loss of weight of each individual organ up to the appearance of death. Death from inanition occurred when the body-mass of a healthy animal fell below one-half of its original weight (to 0.40 per cent.). What was the analogous process of the fever? Does loss of weight here also occur to the same extent as in death due to “consumption”?

In a very laborious and extensive work (Königsberg, 1869, *loc. cit.*) I instituted a great number of daily weighings in fever patients, naturally without especially determining the calory value of nutrition; however, the patients,

¹ Deutsches Archiv f. klin. Med., Bd. vi, 1869. I. Calorimetrische Messungen. II. Wägungen.

² Sur l'inanition. Paris, 1853.

according to the usage of that time, had a strict fever diet administered. The result of this work showed that a fever patient continually loses daily about $\frac{1}{2}$ per cent. to $\frac{1}{3}$ per cent. of his body weight, and that after about six to eight weeks he reaches the limit of inanition. If we reflect that the markedly emaciated body is richer in water and poorer in substance, that the feebleness of the patient may very readily, also previously before the limit of inanition is reached, be the cause of death, we must admit that these investigations correspond with experiences at the bedside and are capable of explaining them. However, upon careful reflection, it was bound to appear that this marked and rapid consumption could not alone be due to the but slightly increased combustion in fever, but that the diminished amount of nutrition in fever, partly due to the loss of appetite in the patient, but caused much more by the withdrawal of food which was previously supposed to be necessary, was the cause of this condition. However, this combustion could not be looked upon as irrelevant, after a certain time it threatened the life of the fever patient. If this was not alone the result of fever but of the withdrawal of nourishment, it could not longer be looked upon as a necessary consequence of the fever, but by the administration of sufficient nourishment an attempt should be made to combat the condition. In contrast to the ancient method of withdrawal of food in fever—"you nourish the fever not the patient"—now the administration of a large quantity of food in fever was the resulting condition.

The first clinician to abandon the old principles was Graves, the celebrated old Dublin clinician who, in his clinical lectures, energetically opposed the prevailing hunger-cure of fever patients. He nourished the patient sufficiently, and in this innovation took such great credit to himself that upon his tombstone he desired the inscription: "He fed fevers." This innovation gained ground but slowly, and up to twenty years ago, in Germany, in the treatment of patients, the principle was maintained, that as long as fever was present but little and diluted nourishment was to be given. Gradually the requirements of better nutrition became prominent. The works of Buss (1878), Hösslin (1882), were followed later by the method of nutrition of patients in my clinic (Therapy of Nutrition). Bauer, in his work upon nutrition of patients in fever, 1883, advised an administration of nourishment sufficient to prevent the decomposition of tissue in fever.

Now the question had to be answered, whether emaciation in fever could be prevented by plentiful nutrition—this was very soon and easily answered—and, further, whether it could be prevented entirely. In my numerous weighings of fever patients, I have had but a single case (a young man with a mild attack of enteric fever), who, in spite of fever, with careful nourishment gained in weight; all other patients lost steadily, but, naturally, by far not to the same extent as would have occurred in absolute abstinence. The important question, whether the decomposition of tissue in fever (consumption) could be entirely prevented by better nutrition, has been decided in a negative sense by numerous investigations; it is not possible at the height of the fever to entirely prevent the decomposition of albumin by an increased administration of albumin, on the contrary, an administration of albumin increased above a certain degree causes increased albumin decomposition.

This uncompensated portion of albumin decomposition, that is to say tissue

decomposition, is not to be referred to the increased heat production in fever, but to a specific action of the fever-producing cause, the bacteria, namely, the toxins produced by them. The increased excretion of urea in fever is partly of toxic origin and this process cannot be prevented; naturally, the remaining portion, which is due to inanition may be compensated for by a sufficient administration of food.

According to these results of scientific investigation, the indication of nutrition in fever has become a quite different one from former views and professional usages. The nourishment does not have for its purpose the reduction of the fever, that is, the prevention of an increase of the fever, but it has for its object the combating of the deleterious effects of the decomposition of tissue in fever and the prevention of a consumption which may prove dangerous. Thus, nutrition in fever is an integral part of therapy, it has become the therapy of nutrition. It assists the drug therapy in many ways. It is capable of strengthening the body of the fever patient in its cells, so that it is able to become master of the cause of fever. Also the formation of antitoxins, and the production of immune bodies which depend upon the activity of the cells, particularly of the leukocytes—which, according to Ehrlich, Wassermann and others, are to be looked upon as of the actual character of immune products—is decidedly facilitated by alimentation.

If, in spite of this, the experience at the bedside shows that the fever is increased by incautious administration of nourishment and that, thereby, in enteric fever, a relapse or recrudescence may be produced, the cause of this is not due to the increase of food in itself, but, moreover, to the incautious administration of nourishment, to indigestion. That decomposition of undigested food may readily occur in this manner, and with this an intoxication, is a fact that cannot be denied and it is evident that an increase in fever may arise from this cause.

In the fever patient the digestion of food is already diminished in the mouth and still more in the stomach and intestines. In the mouth the salivary secretion ceases; mouth and tongue are dry (*fuligo*), mastication is difficult, the stomach is irritable, there is a tendency to vomiting, appetite is absent, not infrequently is there disgust and resistance (for solid food, for bouillon or also for milk). The motor activity of the stomach is also diminished. If the stomach is filled, vomiting may occur. Hydrochloric acid in the gastric juice is diminished (to 0.5 per cent. instead of 2–3 per cent.), and is occasionally entirely absent. On the part of the intestine, fats and carbohydrates are quite well absorbed (Hösslin).

This diminution of the powers by the fever makes it evident that the nourishment of the fever patient must be carried on with great care and that definite knowledge as well as experience is necessary on the part of the physician.

What amount of nourishment does the fever patient require in twenty-four hours? And in what proportions are the nutritive products to be combined so that the total necessary amount shall be present?

For the normal working man, the question of the amount of nourishment necessary in a proportional mixture of the individual food products, has been

decided in that in twenty-four hours he requires 2,500 to 3,000 calories, and this had best be composed of 100 grams of albumin, 100 grams of fat and 400 grams of carbohydrates.

In fever patients the N-excretion is decidedly increased, the increase of the CO_2 excretion, however, as we have seen, is relatively slight; however, the total decomposition of the body in fever is but slightly increased, and we may look upon this increase as from about 10 per cent. to 20 per cent. According to this, the total administration to the fever patient would be estimated at about 3,000 calories, and if we select as a standard the non-working healthy person lying in bed whose calory requirement need not exceed 2,500, we should have to estimate about the same amount for the fever patient. The therapy of nutrition is capable, under favorable circumstances, i. e., if this calory amount can be administered to the patient, in spite of the above-mentioned difficulties which exist in him, of compensating for that part of the total loss which is due to inanition (withdrawal of nourishment). However, it is not capable of completely arresting the decomposition due to fever; in spite of plentiful nutrition in fever patients the decomposition of nitrogen cannot be totally prevented. The attempt has been made, by artificial drug antipyresis (Buss), to prevent or lessen this decomposition in albumin, which, as I have mentioned previously, is due to the toxin action in fever. In this manner also slight success has been attained, but the actual toxic action of the fever even remains uninfluenced in a drug antipyresis. We must, therefore, reckon with the fact: A sufficient nutrition of the fever patient limits fever consumption, but it is impossible for this to be prevented entirely or for the conditions to be reversed, at least in acute fevers.

The mixture of the individual food products cannot be determined from special indications from the nature of the fever. It depends upon the administration of materials capable of combustion, their nature is only a secondary consideration. Fats and carbohydrates are just as necessary as albumin, no one is preferred to the others. A proportional mixture, as has been mentioned, is necessary, but also a mixture of albumin, fat and carbohydrates in almost equal amounts (which, for example, is nearly present in milk) may be designated as entirely favorable.

According to these general fundamental laws regarding the nutrition of the fever patients, the therapy of nutrition in pneumonia must take this into account while considering the special conditions of this disease. The consumption here also consists in the diminished administration of nutrition and in the decomposition of tissue. The first may be compensated for by increased nourishment, the latter is unavoidable. In general, on account of the brevity of the course of the disease, the consumption (emaciation) in pneumonia does not reach a high degree, so that, on this account, as a rule, no direct danger is present. After the crisis convalescence also is relatively rapid; soon decided appetite returns, which rapidly compensates for a loss in body weight. In spite of this, the loss will appear to many to be surprisingly great and compensation relatively slow. I have had many pneumonics weighed to determine the total loss of weight and shall mention some figures. The difficulty of obtaining positive results is probably due to the fact that,

at the height of the disease, patients cannot well be placed upon the scales; it is, therefore, difficult to obtain the starting weight, as well as to determine the daily loss. Only after the crisis, when the patient begins to recuperate, may such weighings be regularly undertaken. In spite of these difficulties, my weighings show: 1, An insight into the total loss of weight due to pneumonia; 2, That the lowest values are observed a few days after the crisis (in the epicritical stage); and 3, That only later an increase occurs, which in several weeks reaches the beginning weight and goes beyond it.

Consumption in pneumonia:

1. Varnisher, aged thirty-one. Former weight without clothes 127 pounds, on the eighth day of the disease 115 pounds approximately, on the twelfth day (day of the crisis) 112 pounds (total loss of weight 15 pounds), upon the twenty-second day 118 pounds, on the twenty-ninth day 124 pounds; discharged cured.

2. B. A., croupous pneumonia. Admitted December 1, 1888, says that prior to his disease he weighed 120 pounds without clothes. Weight upon December 29, 105 pounds (total loss of weight, 15 pounds), upon January 1, 111 pounds, upon January 11, 115 pounds, upon January 19, 117 pounds; discharged cured.

3. E. T., fibrinous pneumonia. Before the disease 129 pounds; upon the twelfth day of the disease 115 pounds (free from fever on the eleventh day of the disease), upon the twentieth day 112 pounds, upon the twenty-seventh day 118 pounds, total loss of weight 17 pounds; discharged cured, weighing 128 pounds.

In severe pneumonia the condition is different, due to the intensity and duration of the fever, which if of long duration will produce greater debility. The danger of collapse, of cardiac asthenia, is combined with the general debility, and at the same time nutrition becomes the more difficult the weaker and the more irritable the digestive canal of the patient. In this case the therapy of nutrition has a more serious and a more difficult task; it must prevent the decimation of strength; the outcome of the disease primarily depends upon its success.

In considering the individual food products which the fever patient, and particularly the pneumonic, is to have, milk stands at the head of the list. Among all foods, milk is particularly suitable for fever patients, it contains all necessary nutritive products in a proper mixture (1 litre of milk contains 35 grams of albumin, 35 grams of fat, of which 31.5–32 grams are absorbed, and 45 grams of sugar). One litre of milk contains 610 calories, 3 litres of milk 1,830 calories. This amount does not quite correspond to the requirement of the fever patient, but it will prove sufficient to prevent febrile inanition. Some patients can take such an amount daily, however, by no means all patients. Not a few patients have an unconquerable aversion to milk in general, in some it produces diarrhea, in some vomiting, many can take but small quantities. I always advise my patients to take milk slowly, and dilute it (with coffee, tea, cocoa). I begin with $\frac{1}{2}$ litre per day and increase as rapidly as possible to 1 litre, and then more slowly to 2 litres, rarely more. If the patient takes daily about 2 litres of milk the nutrition is increased by suitable additions (see below); we may calculate that the emaciation will be limited to the lowest amount, i. e., to the quantity due to the nature of the process (the toxic), decomposition of material.

As additions to milk, if this is not well taken or badly taken, besides the previously mentioned (tea, coffee, cocoa), brandy (10 drops to a teaspoonful to the cup), further, flour preparations which may be cooked in the milk (arrowroot and the like). If there is nausea, vomiting, sensation of fullness in the stomach after the taking of milk, it is advisable to mix the milk with peppermint tea, etc.

Among the additions which increase the nutritive value of milk, besides the previously named flour preparations, milk sugar and cream are to be particularly mentioned. Of milk sugar, at first 50 grams, and if this is well borne, 75 and then 100 grams, are added to 1 litre of milk (the milk sugar is first dissolved in a little water by boiling, and then is added to the milk); this means an increase in value of 410 calories. Cream varies regarding its amount of fat; upon the average 100 cc. contain 126 calories. We administer first 900 milk with 100 cream and endeavor to increase to 750 with 250. Kefyr and koumiss may be employed as a substitute for milk.

Besides milk, bouillon must be mentioned, which is rejected by some patients to whom the smell of meat broth is unpleasant, but is readily taken by others. Its nutritive value is extraordinarily slight, but as a stimulant for the heart and nervous system it is not without importance; the plentiful administration of salt by means of bouillon is also of value. By employing albumin and carbohydrate preparations (somatose, eucasin, neutrose; grits, tapioca, etc.), or with the addition of the yolk of an egg, the nutritive value is decidedly increased.

Flour soups are more nutritive, and, if milk nutrition cannot be used, represent the most important nourishment of the fever patient. An attempt should be made to mix the flour soups in equal parts with milk, or in proportion of 1:3 or 1:4; or, if these milk soups are rejected, omit the milk entirely. For the preparation of flour soups, oatmeal serves the purpose, as well as peas, beans, rice, etc., further, the various infant foods, etc. Addition of albumin preparations, butter, yolk of egg, increase the nutritive value; meat extracts and salt make the soup more palatable. The best prepared soup does not approach the nutritive value of milk, under the most favorable circumstances we can only succeed in attaining one-half of the nutritive value of milk.

Instead of flour soups, porridge may be employed.

Of fluids which simultaneously serve to refresh the patient, there are to be mentioned, carbonated waters, fruit lemonades, buttermilk; further, gluten lemonade, which contains calcium and, therefore, is at the same time nutritious.

Of solid foods, there may be mentioned, gelatin (wine gelatin), stewed fruits, soft boiled eggs, caviar, zwieback (with butter); then mashed potatoes, soft vegetables (asparagus, spinach, grated carrots and the like).

Meat for the most part is rejected by fever patients. As soon as appetite returns scraped meat may be administered, then chicken, pigeon, ham, fish, brain, sweetbread, etc.

Alcohol requires especial consideration. While the law of the association of the diminution of temperature with the withdrawal of nourishment was in full force, alcohol was excluded. With the knowledge of the usefulness of

an ample supply of nutriment in fever, it became more prominent and wine was given in plentiful amounts, especially under the influence of the celebrated Dublin clinician, Todd, who advised large doses of spirits in febrile diseases. Alcohol was given as a stimulant for the heart, as a strengthening remedy, and was also partly looked upon as a disinfecting substance (antiseptic), and after it was shown by experiments that alcohol was capable of reducing temperature it was thought that this measure was entirely rational. In severe cases of pneumonia, (enteric fever, diphtheria) enormous doses of alcohol were given. In the beginning of my practice I was called in consultation to a case of pneumonia in a patient of middle age of robust stature who probably was an alcoholic; upon the seventh day threatening symptoms appeared. I asked what his nourishment consisted of and received the answer: Daily, one bottle of port wine, bouillon plentifully, and gelatinous soups. At the present time we do not give such large doses of alcohol and it is thought that it has rather a weakening action on the heart than vice versa. Nevertheless, alcoholic drinks in acute febrile diseases and in pneumonia cannot be dispensed with and if given in moderate doses they strengthen the action of the heart. The abstinence from alcohol which some physicians fanatically practise on principle should not be extended to their patients—they themselves may do what they choose, but they should not withhold from their patients a refreshing agent which often assists in tiding over serious difficulties.

The correct carrying-out of nourishment is the most important part of nursing. The knowledge and the conduction of nursing is the task of the physician, its execution however, requires assistance, best by a trained nurse. The physician should choose a suitable nurse; she must be thoroughly reliable, she dare not leave a seriously ill person alone for a moment, and must do everything for her patient, administer the medicine, place him in a comfortable position, and must see that there is quiet, air and light. Finally, she must look after an important part of the treatment, the nutrition of the patient. For this, the nurse requires schooling and practice. Food must be administered in an appetizing, methodical manner, and without haste. As a rule, it is now generally accepted that the nurse should give to a seriously ill fever patient every two hours food such as has been ordered or is allowed, therefore, fluid nourishment amounting to about one cupful. Either the patient drinks alone from the cup or the nurse feeds him by means of a feeding cup or spoon (tablespoon, *not* teaspoon).

However, the physician has the ordering and personal conduction of every detail which concerns the treatment of the patient, he must, therefore, regulate and order the nursing in all its essentials. A by no means unimportant part of his activity is the personal treatment of the patient, whose confidence he must gain by quiet determination, care and precision. Simultaneously, I should like to call attention to the psychical therapy which is necessary in dealing with the relatives and friends, primarily the nurses, who should be kept in a good mood so as to serve their patient willingly. More difficult, occasionally, is the treatment of the relatives and friends, the confidence of whom is at least of the same importance to the physician as is that of the

patient. The position of the physician in a severe pneumonia is by no means an easy one. When the severity of the disease continues to increase from the fourth to the seventh day and at its acme takes on a serious character which cannot be concealed from those about the patient, it requires great firmness and self-control on the part of the physician to master the situation. He is to see to it that the course of the disease is not disturbed by anxiety and excitement of those about the patient, and that nothing occurs, by improper measures, or even by absurd procedures, by which the good course of the crisis may be rendered uncertain.

PLAN OF TREATMENT

In treating a case of pneumonia the physician must consider the situation and order everything necessary for the patient; he should select the room and the position of the bed; the room is to be neither too light nor dark; there is to be no communicating room, no noise, and the bed had better be placed so that it may be reached from both sides.

It is self-evident that the patient must be kept in bed.¹ He is to be kept as quiet as possible, avoid much speaking, lie in a comfortable position and not have too many covers placed over him. Food and drink must be given him by a trained nurse. The patient should never be left alone, and special care should be given if he is delirious or attempts to get out of bed. In the main, the various stages of the disease, as regards the indications, as well as special orders, particularly in pneumonia, does not present unusual differences which are worthy of note, and I shall describe them in a few words.

1. *Initial Stage*.—This stage is brief, lasting but a few hours, so that the therapeutic requirements are not definite ones. During the chill the patient covers himself up, lies down, drinks hastily and attempts to sweat. If the physician is summoned he must order rest in bed, reduce the amount of nourishment to fluid food, and not order drugs at all, or if he does, give quite an indifferent remedy. Caution is necessary in administering active remedies at the onset of the disease, as we can never know whether such remedies do good or harm. A laxative brings about amelioration. The diagnosis as yet cannot be made with certainty. Ancient medicine at once ordered venesection to abort pneumonia if possible, or an emetic was given (tartar emetic).

2. *Stadium Incrementi, Development of Pneumonia*.—Regular taking of temperature, saving the expectoration and urine. Physical examination. Therapy even in this time should be withheld. A cooling medicine may be given (muriatic acid or the like), or moderate doses of antipyretics (1 to 2 grams per day). Keeping the patient cool, good ventilation in the room, quiet. Cold applications or packs. The bowels should be evacuated (and the urine). The administration of nourishment is to be methodic, but in the first days it should not be forced, especially if there be a tendency to vomiting.

¹ Sydenham allowed fever pneumonia patients to get up once or twice a day, an indication which may explain the deaths of that period. Besides I have seen this mode with "the old Wolff" (Professor of the Second Medical Clinic) during Schönlein's time.

Fluid food, best milk, in the morning diluted coffee or tea, bouillon, flour soups. If the patient wishes it, he may have some zwieback or yolk of egg, also some soup or meat extract or other nutritive preparation. Fluid may be plentifully administered (water, lemonade, wine with water, tea), but without overloading the stomach, which might lead to vomiting.

3. *Stage of Acme*.—This period of the disease requires great care, for it is at the same time a preparation for the period of crisis. The nearer the disease approaches to the latter, upon the fifth, sixth and seventh days, the more carefully the physician must endeavor to keep up the strength of the patient. Absolute quiet is now necessary, all excitement is to be avoided, even the examination of the patient at this time is to be omitted if there are no particular reasons for carrying it out. Although, as mentioned above, not all solid food need be excluded, the patient in the main should be nourished by fluid food, but this should be in relatively large amounts—the patient should have a cup of milk or bouillon, with an egg or soup every two hours—but without suppressing the appetite or even producing repugnance to food. The stool is to be looked after, which makes the respiration easier and the excretion freer, and the excretion of urine must be encouraged. The latter requires regular observation as a smaller or larger amount of urine is an indication of the amount of nourishment taken; scant, high-colored urine points to bad or even insufficient nutrition.

In the days before the crisis, at the height of the disease, there is usually one or another indication for the use of a remedy, if the pulse is very frequent and small, digitalis in moderate doses (0.25 to 0.5 per day), besides heart tonics, such as tea, coffee (wine with caution!), camphor, benzoin. The use of antipyretics and hydrotherapeutic measures are indicated according to the principles previously described. Morphia (codeia, dover powder) is indicated if there is restlessness and insomnia at this period of the disease. If these indications are not present I am partial to the administration of a preparation of ammonia before the crisis (liquor ammonii acetatis), senega or another expectorant.

At this stage, formerly, blood was withdrawn; in full-blooded patients it would even now be allowable but there is no longer confidence in venesection among the public and in patients.

4. The period of crisis requires particularly careful observation and eventually energetic procedures. With a fall in temperature, in severe cases, not infrequently a serious collapse is combined or is threatened. Dyspnea and cyanosis, beginning pulmonary edema, are the signs of danger, which in severer grades bring about the exitus letalis. Here it is necessary to be on the spot and not to neglect anything. A collapse must be prevented by an amelioration of the essentials of the disease during the latter period before the crisis. In this position we command numerous active remedies which must be carefully chosen and administered cautiously and without haste. Improvement of respiration, strengthening of the heart muscle, amelioration of the fever are the indications. Dry cups serve to improve respiration, inunction of creosote and camphor vasogen; internally expectorants, the preparations of ammonia, benzol, menthol, terpin hydrate. Narcotics must be avoided or very cautiously administered. The bowel must be evacuated.

Cardiac power is increased, that is, maintained by improving the respiration, by the use of the previously mentioned heart tonics (digitalis, caffeine, strychnin), but caution is necessary so as not to shoot beyond the mark.

In more urgent cases (with cyanosis and pulmonary edema) venesection is necessary, followed by the administration of wine (champagne), as well as by the inhalation of oxygen. Further, hot hand and foot baths, eventually infusion of a physiological salt solution, with fruit sugar; inunction and a form of massage may be useful.

Food cannot be forced in such moments. The tortured patient cannot swallow much, filling the stomach gives him difficulty and increases the dyspnea. All the more was it necessary during a previous time to have administered sufficient nourishment at regular intervals.

During this period the physician has a very difficult position, he must watch continuously, must neglect nothing, and yet not do too much. In the presence of the patient and of the friends and relatives, he must retain composure and firmness and must show the greatest interest. If he succeeds in saving the patient from such a threatening danger he is sufficiently compensated for all his trouble.

5. *The Epicritical Stage.*—I believe it to be important to differentiate an epicritical stage, although, in general, it may be said that the patient is saved if he has passed through the crisis. This optimistic view is only correct if nothing is neglected in the epicrisis which has particular conditions, especial dangers and particular therapeutic indications.¹

Investigations of metabolism have shown that the patient who has passed through the crisis by no means at once returns to normal conditions, especially that he does not add organic albumin at once. On the contrary, the nitrogen excretion, as well as the excretion of water, is greatest after the crisis, and, in keeping with this, the patient in this stage by no means at once increases in weight, on the contrary, the body-weight decreases and it is lowest one to two days after the crisis.²

It is because of this condition that the patient is so feeble, often even excited and without sleep after the crisis. The cardiac contractions are feeble, frequent or even slow. During the night, upon an attempt to sit up, palpitation and dyspnea occur. This cardiac weakness brings about an unquestionable danger, in a former time it was the frequent cause of a sudden unexpected death from syncope.

Finally, the appetite and the capability of taking nourishment has not yet improved, not infrequently has the patient refused to take nourishment and the physician cannot force his greatly suffering patient to do so. The indications for this stage are primarily quiet, rest in bed (sitting up strictly prohibited!); in turning in bed, with other necessities, the assistance of the nurse is required. The main thing is, with care and confidence, to increase nourishment, by coaxing, by offering tit-bits (champagne and oysters) to stimulate the appetite. Still it requires usually from one to three days for

¹ *Wunderlich*: After pneumonia has run its course, for some time a careful dietetic régime is necessary (flannel clothing, change of climate, avoiding exertion, milk diet).

² Compare also *N. Svenson*: Stoffwechselversuche an Reconvalescenten. *Zeitschr. f. klin. Med.*, Bd. xliii.

progress. Excitable patients require morphia and should sleep. The examples mentioned at the beginning of this article may be recalled; they show what care is necessary in such patients in the epicritical stage, even after the pneumonia.

6. *Stage of Convalescence*.—If the epicritical stage is separated from the stage of convalescence, the condition of the patient when he enters upon convalescence is much better, rarely presenting great difficulties to the physician. But even here, care is necessary, patient as well as physician may be happy that the disease is over, but the physician must not forget that disturbances and sequels may occur which should be prevented with his best care.

The onset of the stage of convalescence is characterized by an increase of strength (addition of body-weight), good appetite, sleep, all functions of the body being in good order; keep the patient in a good humor.

The last serious question is regarding the first getting out of bed. Positive rules cannot be given for this, but the patient must have increased in his strength and body-weight before this should be allowed. The first rising from bed is an important step to him and should be watched over with all care. If getting up has agreed with the patient he will feel well upon the following day and be in good spirits.

The most difficult part of a clinical lecture is the therapy; for only in the rarest cases can this be carried out with dogmatic certainty. The old clinical school maintained such an authority, in that it prescribed minutely how a disease was to be treated; any deviation was a grave error. But this absolute authority could not be maintained; a program for the treatment of pneumonia cannot be made out. At the present time therapy is an art, or better, the artistic waging of a battle against disease. The weapons for this battle, i. e., the individual therapeutic remedies and methods, may be shown, their manner of action and indications may be described, and, in general, the plan for proper treatment may be indicated—but something still remains, the proper choice and use of remedies suitably and correctly chosen according to the special indications of the disease and the peculiarities of the patient. Under the present complex conditions the practical physician in the special case must himself select what is suitable. The result will always depend upon his personal cleverness and ingenuity, upon his firmness, care, and decision, which are partly the results of good training, but to an equally great degree are qualities of endowment, and dependent upon his own personal culture.

[See also Serum Therapy, page 909.]

TUBERCULOSIS AS AN ACUTE INFECTIOUS DISEASE

(ACUTE MILIARY TUBERCULOSIS, ACUTE TUBERCULOSIS OF THE SEROUS MEMBRANES, ACUTE CASEOUS PNEUMONIA)

By G. CORNET, BERLIN

Tuberculosis is an infectious disease. This truth has entered the flesh and spirit of the present generation of physicians.

The *chronic course* of the disease, which for centuries placed it among the constitutional anomalies, made it difficult to recognize its infectious nature, and the fact that it only manifests itself many months after infection has also been an important element. But even when well developed, in the greatest majority of cases, the affection lasts for years and decades, with exacerbations and remissions, until finally a gradual cure occurs, or more frequently death terminates the affection. Only much more rarely does tuberculosis begin like the other infectious diseases, apparently suddenly, running its course in a few months, weeks, and now and then in days, and then, usually with a lethal termination.

This latter, the **acute form**, will now be considered.

GENERAL ETIOLOGY

Tuberculosis in its acute form etiologically takes a special position among the infectious diseases. While, ordinarily, the outbreak of the disease is to be looked upon as the sign of a *primary* infection occurring from external causes, acute tuberculosis, if at all, depends only exceptionally upon a primary infection. This difference is explained by the biological properties of the microbes in question.

With rare exception, the actual, active infection, under *natural* circumstances, depends upon the entrance and deposition of *but few* germs in the body from without. These few germs, often perhaps only a single one, are capable of producing in a favorable, if I may be permitted to say, specific, appropriate culture media, in a few hours or days, an enormous, massive development, as is seen in the case of the cholera and typhoid bacilli in the intestine, in the pneumococcus upon the mucous membrane of deeply situated bronchi, in the anthrax bacillus in all fluids of the tissues and in the blood, as we see in the bacillus of plague, in the coccus of erysipelas, and others.

The *tubercle bacillus* not only does not possess this property of rapid proliferation outside of the body upon the inanimate culture media which are known to us, it does not even possess it in the animal and human organisms.

In acute tuberculosis there must always be assumed the *pre-existence of a tubercular focus*, in which the number of bacilli necessary to invade in masses must be prepared and then at a certain moment develop suddenly or in briefly succeeding intervals, affecting widely extended areas of tissue in the circulation, in the serous membranes or in the lungs (intrabronchial).

But no rule without exceptions! Cases are known in which, from external causes, the number of tubercle bacilli, sufficient to produce an acute course have entered. Thus, for example, as reported by Schweninger, Tappiener's servant, in spite of numerous warnings, entered the inhalation space in which Tappiener was carrying on inhalation experiments with pulverized sputum in dogs and thus became a classical proof of the danger of such inhalations; the servant, in spite of previous health, perished soon after the dogs that had been experimented upon with the same pathologico-anatomical signs of miliary tuberculosis of the lungs. But! Such cases form exceptions and cannot be compared to *natural* conditions.

Acute tuberculosis does not depend upon a direct exogenous infection, but upon an *endogenous* one, an *auto-infection*, the *prerequisite being formed by a tuberculous focus already present in the body*.

This primary original focus may be *very small*. For example, a single, isolated, primary tuberculous nodule at the surface of the lung may rupture into the pleural space and thus produce a miliary pleural tuberculosis. It may be so small, that it can only be found with difficulty at the autopsy, although the cases in which it cannot be found upon careful search by the trained eye are quite rare. Now and then, however, *circumscribed*, more or less numerous foci, caseous nodules, partly connected, partly quite independent from the explosive focus, are present.

According to this, acute tuberculosis may occur in apparently healthy persons but in those that have a latent focus and then appear apparently as a primary tuberculosis—or after years and decades of suffering it may form the complicating termination of the disease—or it develops in a person who previously has gone through a tubercular attack but was apparently cured.

Recently I saw a young man, who four years ago had a tuberculous apex catarrh, and for two years was apparently cured; he married and four weeks after the wedding, perhaps favored by marked sexual indulgence, was affected by miliary tuberculosis and died; a quite similar case I recollect of a previous experience in which only the final diagnosis was not quite so certain.

As tubercular foci are found in every age, acute tuberculosis occurs at *all ages*, although infants are markedly predisposed.

The different cases of acute tuberculosis are *etiologically* to be considered as one, in so far that in all a sudden dissemination of one or several organs or parts of tissue occurs with tubercle bacilli. *Pathologico-anatomically* and in many respects also *clinically*, they show different phenomena, so that we may differentiate three chief groups: *Acute general*, or a *miliary tuberculosis* limited to one or several organs, *acute tuberculosis of the serous membranes* and *acute caseous pneumonia*. Determining for the variation is the seat of the primary tubercular focus which is the cause of the disease, and depending upon this the method of distribution and the nature of the organs which are

to be considered in this distribution, namely, whether the circulation, the serous cavities, or, in the case of caseous pneumonia, the bronchial twigs are active in the diffusion of the bacilli.

SPECIAL ETIOLOGY OF ACUTE MILIARY TUBERCULOSIS

Acute miliary tuberculosis is characterized by the occurrence of numerous tubercular nodules in the most varied organs, independent of one another and removed from external circumstances, by the entrance of the germs into the *circulation*; the almost simultaneous developing stage of the nodules, however, shows that the invasion occurred quite suddenly, at once or in brief intervals.

Whence come such massive numbers of tubercle bacilli, entering suddenly into the blood, producing almost simultaneously thousands and millions of tubercles? Only two conditions may be thought of: either some individual bacilli which have reached the blood have developed to this extraordinary extent in the circulation or they have at once reached the circulation *en masse*.

In favor of the first view Wild and Ribbert are especially prominent; they believe that, as a rule, only individual bacilli reach the blood and, usually, are rapidly eliminated from the body without leaving a trace, *under very special favorable* conditions of development and an especially increased predisposition they are able to increase in sufficient amounts to produce miliary tuberculosis.

But this theory, above all, is incompatible with our knowledge of the biology of the tubercle bacillus; for we know and are able to demonstrate at any time that tubercle bacilli in the blood and in fluids in general, except upon the surface, do not multiply to a marked extent and, therefore, comparisons and conclusions by analogy with anthrax bacilli and other actual blood parasites are worthless. And how, even in the *circulating* blood, should they be capable of multiplying in such enormous quantities? Besides, in this conception, we meet with so much that is hypothetical, so little that is actually proved, that the objections raised by Weigert, Benda, and by myself are readily comprehended.

Thus only the second possibility remains, that the bacilli in acute miliary tuberculosis enter the circulation *en masse*. For this we also find an *argumentum ad hominem* in the *vascular tubercle* of Weigert in the tuberculous vascular ulcer.

In contrast to the previously assumed immunity of the intima of the vessels from tuberculosis, Weigert in 1877, as is well known, found in veins that were still patulous and capable of function, especially in the large pulmonary veins, tubercles and these *venous tubercles*, were looked upon by him as the sowing point of the seed of tubercle bacilli in the circulation and as the source of acute miliary tuberculosis.

These vascular tubercles may be frequently demonstrated as was shown by the further investigations of Mügge, Schuchardt, Weichselbaum, Bergkammer, Hanau, Hauser, Meyer, Heller, Brasch, Sigg, and others, in miliary tuberculosis, if they are carefully searched for, and besides being found in the pulmonary, as well as in other veins of the body, they are noted in the

arteries, although rarely (Mügge, Marchand, Weigert, Cornil, Schuchardt, Dittrich, Benda, and others), whereas even previously Ponfick had demonstrated to us a third variety of such tubercles, the tubercles of the thoracic duct.

Upon the decomposition of such vascular tubercles, in the formation of tubercular vascular ulcers, unquestionably large numbers of bacilli may enter the circulation—and this is nowhere denied—by constant movement their conglomerants are torn apart and they themselves are disintegrated and widely distributed. This certainly determines *one* way for the development of miliary tuberculosis; that this mode, however, is by far the most frequent, is shown by the almost regular proof of such foci in miliary tuberculosis and only in the case of miliary tuberculosis. Hanau and Sigg's compilation has shown this connection in more than a hundred cases.

Are the cases in which this proof of vascular tubercle was not present capable of causing the entire law to become questionable? No, they are not, on account of the difficulty, the subtlety of such investigations, in which small foci may readily escape the most minute inspection; this is all the more true, for from the moment of the rupture, the ulceration, of the seed, weeks and months may pass before the autopsy, in which the original ulcer may have altered its appearance and must often have undergone changes, so that it no longer appears as an ulcer, but, as Benda has shown, covered by a smooth surface, the shreddy defects of the bacilli-containing caseous masses filled with fibrin deposit or the entire vessel thrombosed, or obliterated and changed into a solid band. What, therefore, is impossible in principle in regard to the condition cannot, as Ribbert has recently required, be looked upon as necessary for an exact proof.

Now, should every vascular tubercle, which may be found in the cadaver, be looked upon as the *starting-point* of an already well advanced miliary tuberculosis, the development of which dates from an earlier period?

ORIGIN OF VASCULAR TUBERCLES

Two conditions are possible regarding the development of the vascular tubercle.

Either the tubercle bacilli grow from a tubercular focus situated in the vessel or lying very near to it, growing *by continuity* into its wall, or they reach it by entering with the *lymph current* and thus gradually attacking the intima.

In this process, however, the development of a true vascular tubercle with consequent ulceration is by no means the *necessary* sequence, for the bacterial toxins diffused from the tuberculous focus into the surrounding areas usually engender an inflammatory tissue ulceration *before* the bacilli themselves enter, which produces thrombosis and obliteration of the lumen of the smaller vessels; in the larger ones, however, the walls are so thickened that a successful resistance is presented to the propagation of the tubercular process and the further entrance of the bacilli is prevented; this can frequently be noted by the strand-like vessels or by some that may even still have retained their function which traverse some pulmonary cavities. In the smaller number

of cases, however, this protection is insufficient, the bacillus enters the intima of the vessel, develops and causes a vascular tubercle.

Or the second possibility: The vascular tubercle owes its development to individual bacilli or to conglomerations of bacilli, which originating from a vascular tubercle previously formed, have reached the circulation, have deposited themselves in the intima or have reached the vasa vasorum and have there been arrested.

Which of the two modes of production, the former maintained by Weigert, the latter by Benda, is the more frequent, cannot be decided at present.

In a similar manner, as in the blood vessels, the formation of tubercles occurs in the *thoracic duct*, only that in this instance, the *lymph* takes the place of the blood.

Although the vascular tubercle is the most frequent point of origin of acute miliary tuberculosis it is not *the only one*, for as investigations have shown, for example a small cavity in a pulmonary vein may rupture (Huguenin, Hanau), or individual arteries imbedded in tubercular glands are proved to be completely surrounded by bacillary areas and the walls filled with them (Koch, Bergkammer, Weigert, Baumgarten, Ribbert), or a wall of a vein is found, as in a case of lupus reported by Demme, showing sieve-like perforations.

The localization of the miliary tuberculosis will naturally vary according to the *seat* of the ulcerated vascular tubercle or according to the point of rupture or erosion. If the anatomico-physiological importance of the individual vessels, their area of supply is remembered, it will become clear that in a disseminated focus all organs of the *greater* circulation supplied from the *left heart*, in case of the *right heart* particularly the *lungs*, will be overflooded with bacilli, whereas for example in a small artery, only the areas supplied by it will form the field of invasion, etc.

In the second variety, *acute tuberculosis of the serous membranes*, a vascular tubercle need not be assumed, instead a proliferating, or, better, a tubercle forming in the serosa and its surroundings that has ruptured, is the precursor and cause.

Acute tuberculosis of the *pleura*, as a rule, is introduced from a focus situated at the surface of the lung, frequently also from tuberculous bronchial or mediastinal glands or by way of the thoracic duct, from a carious vertebra, a rib; less frequently from the pericardium or peritoneum. In case of the pericardium, apart from infection from the pleura, caseous bronchial and mediastinal glands play the chief rôle, but caries of the sternum, of the ribs, the thoracic vertebræ, or rupture of a pulmonary cavity may be the starting-point of the disease.

A *peritoneal* tuberculosis finds its origin in caseous mesenteric and retroperitoneal glands, in tuberculous intestinal ulcers, and especially in the female, in a genital tuberculosis; finally, it may occur by propagation through the pleura.

In all of these instances of rupture tuberculosis of the serous membranes is not the regular but a rare consequence, for in most cases the diffused toxins have caused irritation of the tissue with consequent adhesions of the adjacent

serosa; the ruptures thus cause a comparatively irrelevant condition, it only becomes important when by rapid growth this adhesion has not taken place.

What the circulation of the blood performs in the distribution and dissemination of the tubercle bacilli which have ruptured into the blood current in the case of miliary tuberculosis, is attained in the serous cavities by the mutual displacement of the walls, in the pleura by the respiration, in the pericardium by the action of the heart and in the peritoneum by intestinal peristalsis, and the same results are obtained that we have in view by distributing the seed upon our artificial culture media, namely, an extraordinarily copious growth.

In the third form of acute tuberculosis, *caseous pneumonia*, the general infection is not immediately connected with the rupture of a caseous focus. The latter may have occurred some time before, and in a manner not previously harmful to the organism, thus in the bronchi, so that the caseous masses are evacuated by the respiratory passages without great damage; but for some cause, which will be mentioned later on, the sputum is not discharged but adheres and finds its way into the bronchi which are everywhere present, thence into the bronchioles and into the alveoli and there causes multiple intimately related foci which appear as if joined in a single caseous mass.

In all of the acute forms, as already mentioned, the following *common conditions* occur: Clumps of bacilli which were previously present in the body but which have as yet damaged it but very slightly, as one group limited the others in their action up to a certain extent, now, at once reach a free tract, there to become distributed; in miliary tuberculosis by the blood, in the serous membranes by the friction of the walls and in caseous pneumonia by aspiration into the many-branching bronchi, so that the individual bacillus attains a certain distinctive development and power. To represent this, I should like to say, the deleterious action of about 1,000 bacilli enclosed in a caseous mass shows the same proportion to a similar number of disseminated, isolated bacilli, as the surface of a globe having a diameter of 1,000 mm. is to the surfaces of 1,000 globes having a diameter each of 1 mm., in other words, the latter is infinitely greater than the former.

PREDISPOSING FACTORS

If the causes of the immediate outbreak of acute tuberculosis are asked, if the question is put, why, for example, in acute miliary tuberculosis in one instance, a vascular tubercle develops and ruptures and in another case this does not occur—why in one patient who has been ill but a brief time, or who still harbors a latent focus and not in another person, perhaps an old consumptive, who has been ill for years—if these questions are put, a definite answer cannot be given.

Many of the traditional reasons are only in very loose, accidental connection, others are more the result of the burning of midnight oil than of observation at the bedside. A clear insight is rendered particularly difficult by the great division as to time between cause and effect, which hinders us in the investigation of tuberculosis from stage to stage.

The predisposition of youth for acute tuberculosis, especially of miliary

tuberculosis, may be explained according to the comprehensive description in my text-book¹ that the toxins formed from tubercle readily and more rapidly diffuse into distant regions through the wider and more open lymph passages and lymph spaces; for this reason the inflammatory tissue irritation in the immediate periphery occurs less intensely and thus the entrance of the bacilli into the vessels and into the vascular wall has less hindrance.

Among the predisposing causes those may be most readily explained which are calculated to mobilize the enclosed bacilli in their clump or in a focus; this is favored particularly by *inflammatory saturation*, sudden emaciation and particularly trauma.

Measles and *scarlatina* have quite properly enjoyed the reputation, for some time, of frequently predisposing to acute tuberculosis. The swelling and thorough infiltration of the glands, which occurs in these diseases, are capable of awakening latent tubercular foci; the more rapid absorption of protective proteins in rapid *emaciation* may to a certain extent extract caseous foci; *trauma* by its accompanying inflammatory action may set bacilli in movement or may directly rupture a fibrous capsule surrounding a tuberculous focus and act like a spark in a powder keg. Operations in diseased tissue, for example, upon tuberculous bones and joints, lupus, rectal fistulæ, then pregnancy and especially the puerperal period, rapid resorption of pleuritic exudates and the rapid disappearance of tuberculo-scrofulous glands have also shown themselves as predisposing factors. Climate and weather, as asserted by some authors, have an influence upon the development of the disease.

Similar causes are also invoked as factors in the development of acute tuberculosis of the serous membranes.

The flooding of large bronchial areas with caseous masses by aspiration, *caseous pneumonia* is favored by a bad *type of respiration*, probably with excessive predominant inspiration and insufficient expiration, by weakness and loss of reaction of the ciliated epithelium, properties which may be acquired as well as be hereditary, further by deep breathing, for example, upon forced movements, climbing stairs, or occasionally by respiratory gymnastics during periods at which the sputum in the act of being discharged passes the mouth of open, previously healthy bronchi. By excessive screaming, with succeeding deep inspiration and aspiration, the acute caseous pneumonias may perhaps be explained which are not so rarely noted in the puerperal period in phthisical women.

PATHOLOGICAL ANATOMY

The *pathologico-anatomical* pictures vary greatly in acute miliary tuberculosis accordingly as the distribution occurs by the circulation, into the serous cavities or into the bronchial branches.

In the former case, in acute miliary tuberculosis all or a great number of organs are found permeated by many thousands of tubercles, showing almost the same grade of development, at one time small points scarcely visible,

¹ G. Cornet, Die Tuberculose.—Nothnagel, Spec. Path. u. Ther., Bd. xiv.—G. Cornet, Die Scrophulose, *ibidem*.

or prominent specks the size of a grain of sand, at other times larger hard nodules, completely or centrally caseous, according as to whether death has occurred sooner or later, dependent upon the number of germs, the importance of the affected organs and from the amount of toxin which has entered the circulation. With these there may be noted as witnesses of the former, but less important precursors, now and then caseous nodules having attained some size.

The number of nodules in individual organs and tissues depends partly upon the richness of the *blood supply*, determining above all, however, is the position of the affected organs, that is, the relation of their vascular supply to the causative focus of the miliary tuberculosis.

The *lungs* are most frequently and most severely attacked as their capillary system acts as the first filter for the bacilli-laden blood in all ruptures into the veins of the greater circulation and into the thoracic duct, but they are also involved by their blood supply when ruptures occur into the pulmonary veins.

Upon section the organs reveal a fine, nodular surface, very often dark red in color, the nodules often being surrounded by red areolæ. The spleen and also the liver are often greatly enlarged. Nodules are found further in the kidneys, in the cortical substance, in the medullary substance of the bone, in the thyroid gland, and, what is of value in diagnosis, in the choroidea (in about 75 per cent.), besides also in the mucous membranes, the testicles, in the epididymis and in the prostate gland.

The serous membranes also show fibrinous deposits but they are not so commonly attacked in *general miliary tuberculosis* as the glandular organs which are rich in blood; in the serous cavities a serious, purulent, or hemorrhagic exudate may be found.

Besides tubercles are found in the meninges, especially in the pia, and often besides a turbid, gelatinous exudate. Further, I should like to call attention to isolated infarcts in the kidneys, spleen, etc., and to punctiform hemorrhages, for example, in the brain. The presence of tubercles in the skin will be rarely noted, as unfavorable conditions (cooler temperature) do not allow the nodules to ripen in the short time prior to death. But this condition has been noted by Heller, Peter, Meyer, and others.

In all autopsies it will be necessary to search for the original focus and the point of rupture, in which the topical distribution of the tubercles and the anatomical knowledge of the blood supply may give some points of support; most frequently, as already mentioned, the pulmonary veins and the thoracic duct are the seat of the same.

The vascular tubercle itself appears as a grayish-yellow or white nodule with a somewhat rough, ulcerated surface or, on account of succeeding fibrin deposit, it has become smooth, and now and then, with a polypoid attachment reaching into the lumen of the vessels.

I shall not enter upon the changes which are the result of mixed infection.

Acute tuberculosis of the *serous membranes*, the pleura, pericardium, the peritoneum, shows itself (pathologico-anatomically) by a profuse formation

of tubercles in the affected serous membrane, and besides often by a well developed fibrino-plastic and exudative inflammation. In passing, I must call attention to the varying pictures due to partial adhesions of organs among each other, especially in the peritoneal space, by sausage-like thickening of the omentum, by the formation of thick cicatrices and fresh tubercular deposits in the same, to perihepatitis, perisplenitis, enlargement of the spleen, sacculated exudates, etc., which occur in the more subacute and chronic cases.

In acute *caseous pneumonia* and in caseous bronchitis which belongs to this process, phenomena in keeping with the process by aspiration are found primarily and particularly upon the mucous membranes of the bronchi and in the alveoli. Here and there an entire lobe of the lung appears affected, so closely do the numerous diseased lobules stand together. In consequence of the richness of the aspirated sputum in bacterial toxins, especially if it originates from older foci, do inflammatory exudative processes dominate the field. For this reason there is found a tough exudate rich in fibrin, some desquamated epithelium (giving rise to the former name *desquamative pneumonia*), accumulation of leukocytes and red corpuscles and later on caseous hepatization. Often the tissue decomposes very rapidly (*phthisis florida*) and the formation of cavities occurs.

SYMPTOMS

The clinical symptoms of acute tuberculosis are in part due to a general *intoxication* with tubercle toxins, partly to *local irritative phenomena* and to the *limitation of function* due to the formation of tubercles.

The *intoxication* which appears simultaneously with the distribution of the bacilli, if not even before this, at any rate as soon as the complete development of new tubercles occur, is particularly characterized by *high fever*, *frequent pulse*, *lowered blood pressure* and *great weakness*, briefly, symptoms which show nothing characteristic, but which occur also in other infectious diseases and for this reason not rarely give rise to confusion.

Infections in general maintain a certain cycle in their course, in the manner that the germs of infection in a limited time, develop with relative rapidity to their complete extent, then, however, by exhaustion of the soil which was favorable to them, are destroyed; this gives the entire course of the disease a stamp of a certain degree of regularity.

In *acute tuberculosis*, on the other hand, not only do the number and vitality of the disseminated bacilli vary extraordinarily, but according to the size and age of the focus of origin, the quantity, intensity of the simultaneously disseminated toxins vary; to this may be added, at one time frequent, at another time rare, exacerbations or fresh outbreaks, finally mixed and secondary infections by pyogenic organisms, streptococci, staphylococci, pyocyaneus, and especially in the case of caseous pneumonia with tetragenous, so that every rule is valueless and *irregularity* becomes the *type of the course*.

This may at once be noted from the **fever**, probably the most constant symptom. With or without a chill, the temperature often rises even in the

first days to its maximum, reaching 102° F. to 104° F. It remains at this height, showing a continued type resembling enteric fever, particularly in the case of caseous pneumonia; or it becomes remittent, showing an intermittent type for some days, or in the case of a rapid breakdown, shows a hectic type, with a height of 104° F. with a rapid fall to subnormal, and collapse temperatures. Even in the same patient the fever often changes its character in rapid succession.

More frequently than in other affections, a transitory *inverted type* is noted in acute tuberculosis, therefore, high morning temperatures with evening remissions.

As constant as the fever usually is, now and then it occupies a subordinate position. In cases in which fever was present previously as the result of phthisis or another form of pulmonary tuberculosis, the temperature by the accidental occurrence of miliary tuberculosis, caseous pneumonia or pleurisy may be but slightly raised. A plentiful deposit of tubercles in the brain often brings down the temperature to 100.5° F. and also lower, even causing a more irregular type; in elderly persons as well as in the insane, acute tuberculosis, especially the miliary form, runs an afebrile course, as might occur from bronchitis or in cardiac degeneration.

But even besides this there are cases especially of miliary tuberculosis with relatively low febrile ranges, 100.5° F. This has been observed upon several occasions (for example by Litten), and Josef (from Fürbringer's clinic) reports an absolutely afebrile course, such cases also being reported by Eichhorst and others. This phenomenon apparently does not depend upon the peculiarity of the disease but upon the fact that some individuals, whose heat centres show a certain immunity, either toward bacterial toxins in general or only toward the toxins of tubercles, without improving the course or prognosis of the affection, as taught by the cases quoted above in which death occurred. In a similar manner, we also encounter enteric fever or pneumonia without decided fever.

Vascular System.—The pulse is markedly increased, even in proportion to the temperature; 120 to 150 beats per minute is not rare; with this the pulse is small, soft, now and then dicrotic. The rapidity of the pulse frequently depends upon a compression of the pneumogastric nerve by enlarged tracheo-bronchial glands, to a mediastinitis, pleuritis or pericarditis. Meningeal localization and great age bring down the high pulse frequency somewhat. The *blood pressure* is lowered, an obvious action of the toxins.

In caseous pneumonia not infrequently stasis occurs in the *venous system* which may bring about a lethal pulmonary edema; bulky caseous masses occasionally lead to dilatation of the right ventricle and insufficiency of the tricuspid valve. In miliary tuberculosis, now and then, the signs of the hemorrhagic diathesis, epistaxis, bleeding from the gums, the retina and intestine occur.

No marked changes, at least in acute miliary tuberculosis, are found in the *respiratory organs*, in an implication of the lungs, however, as the result of irritation of the newly formed nodules, upon the terminal filaments of the vagus, severe, stubborn, paroxysmal, usually dry cough occurs which leads

to emphysema; the expectoration is scant, frothy and now and then shows streaks of blood, the respiration is increased to 60, in children to 90 per minute, often accompanied by conspicuously marked dyspnea or orthopnea (irritation of the vagus).

Upon *physical examination* in case older foci are not present, only transitory or no alteration in sound will be noted, later slight tympany may be found, and as a sign of diffuse catarrh, and somewhat exaggerated vesicular respiration, small, crepitant râles. In rare cases, in a very profuse development of tubercles, fine friction may be determined (Jürgensen, Litten).

In acute tuberculosis the signs of pleurisy in general are present, therefore pain, stitch in the side upon breathing, and especially interrupted friction sounds audible during inspiration and expiration, slight displacement of the pulmonary borders, and if an exudate has taken place (not infrequently hemorrhagic) dulness over and a tympanitic note above the same, diminished or bronchial breathing, diminished or absent vocal fremitus.

In tuberculosis of the *pericardium* there is also the well-known friction sound and if the exudate be sufficiently large, increased cardiac dulness, which extends beyond the displaced apex beat downward and to the left.

The most marked changes are, however, frequently found in *caseous pneumonia*, there are besides marked dyspnea over the affected area: dulness, diminished or bronchial breathing, râles, later tympany, metallic, ringing râles and other signs of cavities, which designate the condition which has occurred.

The implication of the *nervous system* in the intoxication is shown by dull headache, vertigo, hebetude, somnolence, apathy, stupor, delirium—symptoms which develop in general tuberculosis, sometimes gradually, sometimes rapidly; only now and then does the mind remain clear up to the end. The cerebral symptoms are increased when the brain itself is the seat of tubercular deposits, in children now and then without this, showing vomiting, strabismus, narrowing then dilatation of the pupils, contracture of the muscles of the back of the neck, convulsions, clonic spasms, continued sobbing.

Further, great lassitude and exhaustion will almost never be absent, as well as great weakness of the emaciated muscles, often combined with frequent sighing and loud cries.

Digestive and abdominal organs. The appetite has almost entirely disappeared, the oral cavity is dry, there is constipation and more rarely diarrhea, and upon implication of the meninges, vomiting. The spleen, while soft in consistence, may be found to be enlarged three to six times its size. Attention will be called to a tuberculous affection of the serous membranes of the abdomen by pain, meteorism, or a tumor, formed by the thickening omentum, or by the signs of a serous, purulent, often hemorrhagic exudate which frequently soon loses its mobility, being encapsulated. Often then, there is also diarrhea and albuminuria.

Upon the *skin* a high grade of *cyanosis* of the face is particularly noticeable, especially about the nose and lips, upon an intensely pale base, and in caseous pneumonia the so-called “cemetery roses” [hectic flush] are noted upon the cheeks.

Besides abundant sweating (and its consequences sudamina and miliaria): herpes, in rare cases even a *roseolar* eruption, erythema nodosum and petechia,

most rarely, however, miliary tubercles upon the skin and toward the final issue cachectic edema in the extremities.

Eyes.—A very frequent symptom in acute miliary tuberculosis, especially upon implication of the brain, I must particularly emphasize on account of its great diagnostic value: The appearance of *tubercles in the choroid*, pale, grayish-white, later yellowish, round or longitudinal specks, often coalescing at the borders, numbering from 6 to 10 and more, which often show pitting upon decomposition (Litten).

Narrowing and dilatation of the pupils, occasionally also retinal tubercular hemorrhages are found also in tubercular meningitis.

COURSE, DURATION, TERMINATION

According to the organ which shows the main effects of the disease and the symptoms resulting therefrom, the course varies greatly. For this reason the individual forms of acute tuberculosis are arranged into subdivisions according to their course. Thus in *acute general miliary tuberculosis* there is a *typhoid form*, in which the *intoxication* is the prominent condition and after a brief prodromal stage shows nervous symptoms, lassitude, high, slightly remittent fever, rapid pulse and increased respiration, dyspnea, delirium, further decided enlargement of the spleen, an eruption resembling roseola and diarrhea, the course closely simulating enteric fever.

Then the *pulmonary form*, in which besides the fever, distressing cough, chest pains, excessive increase in the pulse and respiratory frequencies, marked dyspnea, orthopnea and cyanosis are prominent; the physical signs also calling attention to disease of the lungs, so that the thought of a pneumonia or of a severe bronchitis, especially in the aged, arises.

Now and then, however, irritative phenomena on the part of the brain mask all other existing symptoms. This is the *meningeal form*, showing itself by unbearable headache, apathy, stupor, delirium, spasms, strabismus, whereas pulse and temperature are less markedly increased and very frequently, in deep coma there is a peculiar and increased respiration (v. Strümpell), or deep sighing inspiration betrays the respiratory difficulty.

Now and then cases occur which run a fulminant course or such as resemble delirium tremens and a malarial intermittent or a pure pharyngolaryngeal disease (Catti).

Among the acute tubercular diseases of the *serous membranes* those of the *pleura*, the *pericardium* and the *peritoneum* must be differentiated from each other; further, according as to whether the tubercle formation or the inflammation, brought about by toxins and mixed infection, is most prominent, therefore between a *dry* and an *exudative* form with numerous intervening stages, in which the latter are again subdivided regarding the composition of the exudate into a *serous*, purulent, and, as occurs more frequently in tuberculosis than in other affections, into a *hemorrhagic* form.

Not so rarely does a peculiar combination of a tuberculosis of several serous membranes occur, which has been particularly studied by Vierordt. Whether the onset of the affection be in the pleura or in the peritoneum, added to the tuberculosis of one serous membrane that of another one is joined,

either early in the course or only after the first affection has retrogressed. The course is commonly subacute or chronic rather than acute, mostly exudative, sometimes resembling the typhoid type, at other times, however, entirely afebrile.

Caseous pneumonia, galloping consumption, is characterized by an excessively rapid course and destruction of tissue, probably depending upon a mixed infection.

Acute tuberculosis may begin with general malaise, unwillingness to perform bodily or mental labor, vertigo, mental depression, weakness, slight rises in temperature—according to its seat also, with troublesome cough, pain in the chest, abdominal pains, diarrhea, cardiac palpitation, therefore *gradually* with a prodromal stage, or in a person already the subject of chronic tuberculosis and especially in elderly persons, by a *scarcely noticeable increase* of the previous symptoms, a transition into the acute stage occurs, or finally, the affection appears suddenly, like a thunder-storm from the clear, unclouded sky.

The **termination** of acute tuberculosis, at least of general miliary tuberculosis, is in death, as a rule, even although timely variations occur in the course, transitory improvement which represents a temporary arrest and excretion of the toxins previously formed in the body, and even actual improvement in intervals of from one to two months with apparent convalescence and actual well-being (Reinhold, Henoch). Now and then a transition to a more chronic form occurs, and exceptionally recovery takes place in miliary tuberculosis.

The possibility of recovery was maintained by individual physicians some decades ago, but denied by the majority; but since Freyhan and Henkel's observations, the cure of a bacteriologically determined meningitis must be admitted; in the other forms of acute tuberculosis, without allowing ourselves to be too sanguine, the possibility of cure cannot be denied.

Somewhat more favorable is the termination of tuberculosis of the serous membranes; a transition into the chronic stage and even complete cure is not so very exceptional. As is well known, particularly in peritoneal tuberculosis, a favorable outcome in the last few years has been noted spontaneously and relatively often under the influence of laparotomy.

In this instance, as in the case of caseous pneumonia, it depends upon the amount of the bacilli and toxins distributed, upon the extent of the affected area, the intensity and acuteness of the process, whether there may be hope for cure or not.

The **duration** of a *manifest acute tuberculosis* varies from days to months. There is even, to a certain extent, an ambulatory form in which the patient up to a few days, even a few hours before death does not present symptoms. Thus, Demme reports the case of a girl aged five years, who was apparently quite healthy, during play was attacked by convulsions and died two and a half hours later, the autopsy showing widely distributed miliary tubercles. There are also cases known in which patients up to a few days prior to death were still carrying on their military duties (Grawitz). Upon the average, well developed miliary tuberculosis, especially if the brain is but little implicated, is from six to eight weeks, otherwise the period is briefer; tuberculosis

of the serous membranes lasts, provided an extensive exudate does not cause a rapid fatal termination, two to three months and longer (naturally in these cases an acute course can no longer be considered). About the same length of time, five to twelve weeks, is the duration for the very acute form of caseous pneumonia. *The cause of death* is the general intoxication by the toxins, the resulting general exhaustion and cardiac asthenia, further, insufficiency of respiration by a limitation of the respiratory surface, whether it be due to miliary tubercles, to an exudate, to caseous infiltrates or to pulmonary edema.

DIAGNOSIS

In the diagnosis, according to the form of acute tuberculosis which is present, there are some very important and accurate diagnostic aids.

In general miliary tuberculosis, due to the rupture of bacilli into the circulation, the best proof consists in the finding of tubercle bacilli in the blood, which, for this purpose, may be taken by means of a capillary tube from a previously disinfected tip of the finger which has been pierced, or by a wet cup (Weichselbaum, Meisels, Lustig, and Rüttimeyer, and others). Naturally, in this investigation all other aids will be called into use, dilution, centrifugation, cultivation upon Hesse's culture media. But the demonstration of tubercle bacilli in the blood is a very fortunate accident, and the test will most often prove negative, as even in well developed miliary tuberculosis the tubercle bacilli are not found during the entire course of the affection but only during the period of rupture and a short time afterward, later being deposited here and there, hence disappearing from the blood.

If decided meningeal symptoms point to an implication of the meninges, the attempt may be made to determine the diagnosis, with certainty, by the demonstration of tubercle bacilli in the cerebrospinal fluid, according to the processes of Lichtheim, Fürbringer, and Dennig.

Further, as the third key for the diagnosis, the frequent occurrence of choroid tubercles should be remembered, which may be readily demonstrated by the ophthalmoscope, pointing definitely to an infection of the brain and with great probability to a general dissemination of tubercle bacilli.

Also the occasional appearance of miliary tuberculosis upon the visible mucous membranes, especially in the pharynx and larynx, should be remembered.

Bacilli in the sputum will but rarely assist the diagnosis of miliary tuberculosis, however, in caseous pneumonia they are often decisive. In the urine and feces bacilli are found but rarely and then only in old processes.

DIFFERENTIAL DIAGNOSIS

The principal difficulty will occur in a *differentiation between miliary tuberculosis and enteric fever*. First, the valuable Gruber-Widal reaction should be thought of, although in rare cases and to a slight extent it also occurs in persons not affected by enteric fever, or remains for some time after the attack has run its course and it may even be absent in enteric fever for

a period, nevertheless, in case the reaction occurs rapidly and energetically it is to be looked upon as a positive sign of enteric fever.

This reaction would find an analogy in the Courmont's serum reaction for tuberculosis, but there is still doubt regarding the accuracy of the latter; according to the investigation of different authors (for example Beck, and Lydia Rabinowitsch), further investigation is necessary. A parallel is also found in the determination of tubercle bacilli in the blood, as in the case of typhoid bacilli in the blood, in the urine or in the feces (Piorkowski's culture media). If all of these methods of investigation prove negative the development and course of the disease must be utilized for diagnostic purposes.

[It would appear from a careful review of the various reports in the literature that the serum diagnosis of tuberculosis of Arloing and Courmont has continued to yield irregular results, and such value as it may have is obtained only when it is used by those fully instructed in every detail of the technique which these investigators have themselves employed.—ED.]

In this connection, the history may give important points, on the one hand, the presence of an epidemic of enteric fever, or at least the occurrence of several cases in the neighborhood. On the other hand, the simultaneous occurrence of tuberculosis in the family of the infected individual or dating back but a few years, the so-called pseudo-heredity which still plays a great part especially in young persons who reside in the family circle. Still more important, if the history shows that the affected individual has suffered previously from tuberculosis of any variety and localization, from tuberculo-scrofulosis, or if it be possible for the physician to still demonstrate a tuberculous focus anywhere in the body which has perhaps formed the starting-point for a miliary tuberculosis; above all, I must advise the most accurate investigation of the apex of the lung for small foci.

The course of the disease presents diagnostic points of support in so far as, for example, a comparison of the catarrh present with the disproportionate dyspnea, or cyanosis favors tuberculosis, as well as an unusually great pulse frequency which only does not occur upon a marked implication of the brain.

In favor of tuberculosis is the non-characterized atypical and, as a rule, not very high fever, especially of the inverted type, whereas in the case of enteric fever there is a regular transition from the continued to the remittent, and later to the intermittent type.

Dicrotism is rarer and more transitory in tuberculosis, diarrhea is not very frequent and then does not present the peculiar pea-soup stools, enlargement of the spleen is less constant, often less marked, less palpable, and, finally, does not occur so early (in enteric fever in the first week). A roseolar eruption is exceptional and occurs less in crops (in enteric fever about the middle of the second week). On the other hand, the cough is more intense, the catarrhal phenomena earlier and more intense, the pulse usually softer.

The tongue showing red borders in the first week, in the second week profusely red, hemorrhages from the mouth and nose and accidental parotitis, *favor enteric fever*. On the other hand pericardial or pleuritic friction sounds, early loss of strength and cardiac asthenia *favor tuberculosis*.

Nevertheless, cases may occur as reported by Senator, Eichhorst and others, which may even be mistaken by the most prominent diagnosticians. To this

must be added that miliary tuberculosis may develop at the height of an enteric fever infection.

From confusing miliary tuberculosis with bronchitis of old persons, with capillary bronchitis of children, with pneumonia, malaria, pyosepticemia, acute mania, only careful observation of individual symptoms will offer protection.

In the diagnosis of *acute tuberculosis of the serous membranes* in general, the signs of a pleurisy, of a pericarditis must be considered. To determine the specific tubercular character of the affection the decidedly prominent intoxication phenomena, especially in the acute form, will prove valuable. The history and the determination of another tubercular focus serve to point the way; in case of a pleurisy, the apex of a lung or a supraclavicular or cervical gland, in peritonitis the genitalia, in the uropoietic system or in the intestine or its adnexa. The hemorrhagic nature of the exudate favors tuberculosis (or carcinosis).

Especially in pleurisy, the high-graded cyanosis and dyspnea, with a comparatively slight exudate, point to tuberculosis.

In favor of peritoneal tuberculosis is a palpable strand-like thickened omentum, early encapsulation of the exudate and, finally, an accompanying cirrhosis of the liver.

The most certain conclusion can naturally be drawn by the *demonstration of bacilli* from the exudate obtained by puncture. A negative result, however, proves nothing, for, as is well known, even in a well developed tubercular exudate, frequently no bacilli are found. In my opinion, the reason for this circumstance is the absence of motility of the tubercle bacilli, so that they fall to the lowest areas of the exudate as well as in culture media.

By shaking, the bacilli may be distributed in the culture fluid. As this is not possible in man, I have lately employed a little artifice which in one case gave me very conspicuous assistance.

After I had searched, without result, for tubercle bacilli in the exudate obtained upon two occasions in a case, which in my opinion was unquestionably tubercular pleurisy, I punctured the same area again. In using a 10-gram Koch syringe I pulled out the rod and then quite forcibly pushed it forward again, opened carefully and repeated this maneuver three times.

Only in the exudate obtained upon the fourth withdrawal after it had been centrifugated, did I detect quite a decided number of tubercle bacilli. Perhaps this method may be of further use; but I must particularly emphasize, that I only regard this method as available, if it is carried out under strict aseptic precautions and the syringe is surgically clean. Koch's syringe, in this respect, I regard as most serviceable, if the effort is made to become perfect in its use.

In the diagnosis of *acute caseous pneumonia*, the demonstration of bacilli in the sputum is decisive. The correct path would be found if in considering the history (a pulmonary affection already present) the constitutional phenomena of an intoxication and the physical signs (dulness, diminished and bronchial breathing, later tympany and cavity symptoms, râles) are combined. A confusion with chronic bronchitis, with or without emphysema, or with chronic pneumonia following influenza, can scarcely occur in the acute form of tuberculosis; acute caseous pneumonia can scarcely be confounded with

pulmonary abscess and pulmonary gangrene, first on account of its mode of development and its course and then by the characteristic symptoms of the previously mentioned diseases (the evacuation of mouthfuls of sputum, shreds of lung tissue and sputum, fetid odor of the same).

The differentiation from pulmonary syphilis can only be difficult in the more chronic cases. If no tubercle bacilli are found after a long period, if the affection occurs in the neighborhood of the hilum, especially in the right middle lobe, the affection running its course with slight fever, syphilis should be thought of. The history, the finding eventually of syphilitic residua, and finally the result of an antisyphilitic treatment, determine the diagnosis.

Cancer of the lung, echinococcus, actinomycosis, will scarcely ever resemble acute tuberculosis. In a questionable case the examination of the sputum (either containing tubercle bacilli or malignant elements, echinococcus hooklets, constituents of cysts, ray fungi) will give the decision.

I have already mentioned **prognosis**. I should only like to emphasize, not to entirely give up hope in acute tuberculosis, and, above all, not in the case of caseous pneumonia and in tuberculosis of the serous membranes, for an active therapy is by no means without importance in the outcome of the disease.

THERAPY

Therapy has for its object maintaining the strength of the body and attempting to convert the acute stage into a chronic one. The first duty is the most careful observation of correct hygiene; air, free from dust, pure air in the sick-room obtained by thorough ventilation, cleanliness, etc., and the administration of plentiful nutritious nourishment, this being suited to the power of digestion which has often been weakened by the fever.

Great attention must be paid to the *heart*: Stimulants, alcohol, camphor are valuable in strengthening its power and energy.

For the *fever*, the best remedy is strict rest in bed (which is quite obvious in such a severe condition). In acute tuberculosis it will be rarely possible to suppress the fever by rest alone; a hydriatic treatment (sponging with vinegar water, wet packs, etc.) and drug treatment must be used. The latter I only advise when the fever produces decided damage (for example anorexia).

First among the antipyretics in tuberculosis is probably pyramidon, as it does not damage the heart.

The morbid focus is rarely susceptible to our treatment; only in tuberculosis of the serous membranes the remedies employed for pleurisy and peritonitis should be used.

The pains, dyspnea and cough must be combated with narcotics; especially in desperate cases we need not be sparing with these remedies.

In general it may be considered that with every day that is gained the possibility increases of changing the acute into a chronic stage.

[See also Serum Therapy, page 909.]

ACUTE ARTICULAR RHEUMATISM

By CH. BÄUMLER, FREIBURG

HISTORY

YEAR in and year out, in the wards of our hospital, as in any other large hospital, a by no means small number of cases will be found in which the freedom of movement of the patient is limited by pains, especially in the region of the joints, and by swelling of the joints, in which the motion has entirely ceased because of stiffness. If such patients are asked what troubles them, the lower classes answer that they have pains in the limbs, educated persons, that they are suffering from "gout" or from "rheumatism," or if there are patients that pay attention to what physicians say in their presence, they may even make a differentiation between "muscular rheumatism" and "rheumatism of the joints."

With this word "*rheumatism*," by which so much is designated and which in some parts of Germany has even retained its literal translation "flow" (from $\rho\acute{\epsilon}\omega$, I flow), we have the remains of one of the oldest theories of physicians regarding the appearance of morbid processes in the body. The flow of spoiled fluids from the brain to other parts of the body, the external excretion of the same from mucous membranes ("catarrh") was looked upon in antique medicine as the principal cause of disease.

In the course of time this view concentrated itself upon more distinct groups of disease, and in our time the word "rheumatism" only designates morbid conditions which are principally characterized by pains, having especially a variable property, with or without distinct inflammatory phenomena. As such pains frequently have been noted following a determinable *refrigeration* of the surface of the body by draughts, wetting, etc., many morbid conditions that have appeared after such "refrigeration" have been designated as "rheumatic."

The expressions "rheumatism," "rheumatic" are used to-day in a symptomatic as well as in an etiologic sense. But this is just the reason why many entirely different diseases are combined under these designations. If the different cases in which the patients come to you with a diagnosis "rheumatism" are examined it will be noted without difficulty that important differences are present, which permit the arrangement of these determinable morbid conditions into quite distinct, well-known pathologico-anatomical groups, and in place of a vague designation which actually expresses nothing, we can make a correct diagnosis.

Let us examine the following history, a woman complaining of "rheumatism" in the arm and in the neck. This old lady has the appearance of a cyanotic condition due to a circulatory disturbance arising in the heart.

The examination of the affected arm shows normal joints, no swelling anywhere, but upon certain active or passive movements, there suddenly appear severe pains which radiate toward the hand or toward the back of the neck. If the course of these pains is followed, it will be found that there are quite distinct areas above the clavicle, upon the ridge of the shoulder, upon the upper arm, that show an extraordinary sensitiveness upon very slight stretching, or develop punctiform painful areas upon pressure. These points correspond to certain areas in the course of *sensory nerves*, and, on account of this, as the further examination shows, we arrive at the conclusion that the condition which the patient has designated as rheumatism is a circumscribed disease of distinct sensory nerves, which is probably favored and maintained by the patient's tendency to circulatory disturbances, and that we are not dealing with "rheumatism" as the patient believes, but with a "*neuralgia*," the anatomical substratum of which, probably on account of the symptoms present, may even be designated as a "*neuritis*." These changes are not rare in sensory nerves, often in the area of very superficially situated cutaneous nerves, as the result of refrigeration, and occasionally a very small nodule, painful upon pressure, may be found under the skin, from which the pains radiate, which the patient, and perhaps also the physician who is consulted, designates as "rheumatism."

Or let us take another case, a patient who from time to time is bothered by severe pains which he believes are due to changes in the weather; they compel him to take to bed, the pains suddenly occur in the region of the knee and ankle joint, but disappear very rapidly or may even radiate, similar to neuralgic pains. If the patient is free from pain he may be out of bed and walk about. But the peculiarity of his gait is conspicuous, he throws his feet forward to an unnecessary degree, and in bringing down the heel he expends just as much unnecessary force. We recognize this gait as the typical ataxic gait, and know that the same is a frequent and important symptom of tabes, a disease of the spinal cord. In spite of the fact that the patient has pains in the region of the joints, which he perhaps refers to frequent refrigerations or to a damp dwelling, before the physician makes a diagnosis of "chronic articular rheumatism" he will notice the peculiarity of the gait and have a suspicion that the patient is suffering from tabes, and further findings will make his diagnosis certain. In these presumed "rheumatic" pains the condition is due to central, so-called *lancinating pains of tabes dorsalis*.

In our women's wards a girl was present for some time on account of inflammation of the throat, with fever; she related that she had been suffering for some time with "gout in the head," and also rheumatism in the legs. The severity of the pains in the legs and the immobility due to this cause could easily be referred to articular rheumatism. It was conspicuous that the pains occurred with severity during the early hours of the night. An examination of the throat showed that no common form of angina tonsillaris was present, but that a round ulcer with markedly reddened and raised borders could be seen in the midst of an inflammatory swelling on the posterior wall of the pharynx. Several regions upon the head were very sensitive to pressure without showing any other changes; in the legs, especially the anterior

surfaces and the borders of the shins were the points that were the seats of pain, and pressure, especially in some few flatly raised surfaces, produced pain. The joints were not implicated. Upon the forearm there was an ulcer about the size of a twenty-five cent piece, with a crust resembling an oyster-shell.

Upon being questioned in regard to a small scar upon the bone, producing some depression of the forehead, the patient related that several years ago she suffered from similar pains, that at that time a tumor formed upon the forehead, and was opened by the physician.

Upon the basis of all these phenomena, and after a careful examination of the entire case, we arrived at the conclusion that this was a case of tertiary syphilis. In regard to the pains in the legs, these were due to a *syphilitic periostitis*, and we were able to convince ourselves of the correctness of the diagnosis by the rapidity with which the symptoms ameliorated under proper treatment. Pains and fever disappeared in a few days after the use of potassium iodid, the ulcer in the throat healed as did also the area upon the forearm, and after a few weeks the previously pale, cachectic patient had assumed the appearance of a blooming, healthy young girl.

Cases of this sort are not so rare, and in any stage of syphilis, pains resembling articular rheumatism may appear in the head and limbs. The similarity of the phenomena, especially if implication of the joints occurs, may even be so great that "syphilitic articular rheumatism" has been spoken of. In such instances anti-syphilitic treatment causes the symptoms to disappear with amazing rapidity.

More frequent than cases of this kind are others in which rheumatism is spoken of, and especially "**muscular rheumatism**," as in the case of a patient, who, after sweating at laborious work, sits in a draught and immediately develops a "stiff-neck" so that he must keep the head quietly in one position, as the most severe pains occur in that side of the neck upon the slightest movement.

Similar consequences may follow great stretching of a muscle or an extraordinarily marked contraction of a muscle group which develops immediately the severest pains in the lumbar region, as may occur in the case of laborers that lift a heavy stone in a stone-quarry.

In such cases, tear of the muscle or, if refrigerations have been the cause, vascular dilations or circulatory disturbances of the muscle and even a slight degree of inflammation may be present. Such conditions must be thought of if, after a prolonged period of severe muscular activity, not only a sensation of tiredness but actual muscle pain occurs after each use of the muscle in question, a certain time being required for these symptoms to disappear. Any one that has learned to ride horseback will remember that for days the first riding attempts were followed by pains in the adductors of the thigh and in the pectoral muscles.

After such painful conditions we should look along the course of the muscles themselves for changes which are the cause of these phenomena, we must search for the exciting cause and then make our diagnosis. Under some circumstances a case may occur that will at first be designated as muscular, and even also as arthritic rheumatism, which, upon careful examination, will

prove itself to be an "infectious muscular inflammation" or even also as trichinosis.

The designation "rheumatism" is, however, most usual for diseases of the *joints*, for acute as well as for chronic ones. Here also in the course of time we have learned to differentiate, especially after reflecting upon the causes of the various affections. A tuberculous or syphilitic arthritic or osseous inflammation will no longer be called arthritic rheumatism, a gonorrheal joint-inflammation will be diagnosticated as such and we will no longer content ourselves with the vague diagnosis "arthritic rheumatism" but institute the proper treatment in such instances. An inflammation affecting the joints, arising in the form of septicopyemia, affecting two or more joints, will be designated as a metastatic-pyemic articular inflammation, and not as articular rheumatism.

Thus the designation "**articular rheumatism**" has gradually been more and more limited, and it should be our endeavor in the individual case not to be satisfied with this diagnosis but to attempt a representation of the changes present and of the causes that have given rise to them, and then to designate the disease after the result of the closest scrutiny. Then, especially in chronic joint diseases, but a small number of cases will remain in which a far-going characterization according to our present knowledge or perhaps during the time of the first examination will still be possible. To this small remainder of morbid conditions, for the present, the designation articular rheumatism should be limited, and to these only where the phenomena of a well-characterized form of acute or subacute, in rare cases a chronic multiple arthritic inflammation, the actual cause of which is at present not known, are manifest.

We intend to occupy ourselves from now on with this form of disease, articular rheumatism in a restricted sense, and especially in its acute and subacute forms, "*rheumatic fever*," "*polyarthritidis rheumatica acuta*."

As the Greek name already tells us, as a rule, there is an implication of numerous joints. By some a mono-articular form of the disease is assumed, but it is very probable that an inflammation limited to a single joint is for the most part due to other causes.

SYMPTOMS

We shall first describe the *clinical picture* of acute articular rheumatism. Usually, quite suddenly, often after a marked refrigeration occurring from any cause, and accompanied by high fever, there develops a painful stiffness in the entire body, in the limbs not less than in the back and in the nape of the neck. The more movable in itself the portion of the body attacked, the greater will be its implication, as the most movable parts can never be kept entirely quiet even in complete rest. Thus, it may occur that, because of the slightest movement giving rise to severe pains the patient may lie immovable like a log in bed in the course of the first few days of his illness, so that if, as is usual, the joints of the arm, hand and fingers are affected, he will require help even in eating and drinking. The pains, which are especially severe upon movement of some joints that are more markedly implicated,

and are even more permanently present in quiet rest, are differentiated by their severity and also by their seat from those very annoying pains which any high fever brings about in the most varied morbid conditions without an affection of the joints. These febrile pains are a kind of painful fatigue with a sudden flaring up in the body, at one time here, at another time there, alternating rapidly, frequently increased by the slightest external cooling, then combined with a sensation of chilliness, being tearing or stabbing in character, for which among the laity and even among physicians the designation "rheumatic" pains is used, or are evidently even of a neuralgic nature, perhaps they may even be due to a central cause. They have nothing in common with rheumatism but may accompany this as well as any other febrile affection.

The continuous pains which are present even during complete rest are due to the *inflammatory swelling of the articular regions*, above all, to tension which occurs in the articular capsule by an effusion of fluid stretching it. The affected articular region shows all the symptoms of an inflammatory effusion of fluid into the joints, redness and increased temperature of the skin, occasionally also some edematous swelling of the subcutaneous cellular tissue. In the large joints which are not surrounded by muscles, the increase in the synovial fluid may be determined by fluctuation; at the knee joint this may be recognized by the so-called dancing of the patella. Even in the small joints of the fingers the effusion may be easily determined. The sheaths of the tendons which are near the joints, especially those of the fingers, may also be implicated in the inflammation, and just so the nerve-trunks which are in the vicinity of a joint, for example, the sciatic in an implication of the hip-joint may be affected by the inflammatory disturbance in circulation. Then pains which radiate to some distance from the joint, affecting the point of distribution of the sensory nerve, may be accompanied by the true arthritic pains.

Among the most frequently affected joints are those of the *jaw*, perhaps on account of their constant use. Their implication may almost prevent the opening of the mouth and thus cause the administration of nourishment to become very difficult. The small joints of the larynx, and even the very much smaller ones of the internal ear may be the seat of the rheumatic inflammation.

A *continued marked secretion of sweat* is very characteristic of the disease. The perspiration has a peculiar acid smell, and, in fact, shows an acid reaction.

The same reaction is also shown by the decreased excretion of fluids from the mouth, by an acid decomposition of the desquamated epithelium of the mouth, which occurs in large amounts upon the surface of the tongue. On this account the tongue shows a thick creamy coating, which becomes brownish if the patient breathes with open mouth, and upon a more prolonged mouth-respiration it becomes black. Upon the whole, however, this dryness of the surface of the tongue and mucous membrane of the mouth is more rarely seen in acute articular rheumatism than in other affections that are accompanied by high fever. This is due, above all, to the fact that we possess to-day a number of remedies by which, with an early and sufficient administration in acute articular rheumatism, the high temperature of the body and the articular inflammations are very rapidly retarded, so that continued high fever is only exceptional and is only noted in complicated cases. A tongue that has transi-

torily become dry may therefore, apart from its coating, rapidly again become normally moist. Under special circumstances, due to organic changes causing nasal breathing, there may occur in the case of acute articular rheumatism, even with but moderate fever, a condition of marked dryness of the surface of the tongue, with a fuliginous coating, with fissures and inflammatory swelling due to these causes. Then if secondary infections occur from the mouth—primarily into the respiratory passages and into the lungs—a clinical picture may develop such as is sometimes seen in the case of enteric fever, the morbid picture which we designate by the name “status typhosus.”

But these are rare occurrences, only appearing from the accidental presence of various unfavorable circumstances. Nowadays the cases are few, in which the joint inflammation is not retarded and the fever decidedly reduced in four or five days, if it has not disappeared entirely by treatment with the salicylates. Fortunately, to-day, on account of our methods of treatment, articular rheumatism shows an entirely different picture from that which I was accustomed to seeing during my student days. For weeks the patient would be in bed with the phenomena previously described, and, unless nursing was particularly careful, bed-sores would develop, frequently enough the sweating would favor a miliary eruption (*miliaria rubra* or *alba*), which upon some portions of the body or in obese patients would produce an eczema, and, by causing itching which could not be borne, would add fresh tortures in addition to the joint pains and the immobility.

But in spite of the gratifying change which the treatment with the salicylates and other preparations has brought about, acute articular rheumatism is still to be regarded as a serious disease, which frequently enough throws its shadow over the entire remainder of the life of the individual, not rarely cutting it short. For, in spite of these active remedies which we now control, we are not able to prevent all of the manifestations or complications of the disease, about which more will be said in detail.

Even without especial accompanying phenomena or complications, it was formerly noted in the very prolonged course of the disease that the patients were greatly debilitated, lost flesh and became conspicuously anemic. Insufficient nourishment on account of incomplete anorexia, difficulty in taking food, if pains were present in the jaw or if the laryngeal articulations were affected, gave rise to pains in deglutition; the continued arthritic pains and the loss of sleep due to this cause, the forced immobility and the fever are the causes of a rapid disappearance of fat and muscle. To judge by the rapid emaciation, the process of combustion in rheumatic fever is especially increased. The height of the temperature on account of the cooling which is due to sweating and evaporation of the sweat, is not sufficiently demonstrated by the thermometric records of the body-temperature. Such examinations of metabolism as we possess in the case of enteric fever, especially regarding urea and carbonic acid excretions, have not been made, as far as I know, in the case of acute articular rheumatism. The explanation would be found in the emaciation which increases from day to day and in the conspicuous pallor which remains after the fever disappears.

The disease also shows an exhausting action in another direction, which is much more important than that indicated by the thermometer regarding

the temperature present. It shows itself in that here and there exhaustive conditions occur in the central nervous system, which are similar to those arising in septic diseases that run their course with high temperature, or similar to those occurring in enteric fever in which there is long-continued high fever. Here the normal regulation of the body heat suddenly ceases, at times an overheating of the entire body occurs, *hyperpyrexia* develops, the temperature sometimes rising to 107.6° F. and higher.

Whether in this hyperpyrexia which occurs in the course of acute articular rheumatism or in other febrile diseases, or also in certain severe neuroses in which hyperpyrexia sometimes appears, particular toxic substances form, which produce a paralyzing action upon the centres which control heat regulation, or whether the condition is due to exhaustion of the affected ganglion cell groups in consequence of a too prolonged extraordinary exertion, is as yet not known. But the fact should be remembered that particularly in acute articular rheumatism and not only in the severe cases but also in milder cases, hyperpyrexia is occasionally noted. This may even occur during a period in the disease in which the patient is close to convalescence. A condition of this kind in which usually with a rapid rise of temperature coma occurs suddenly and the entire clinical picture resembles an attack of sunstroke, is extraordinarily serious and can only be occasionally combated by the most energetic external cooling of the body. Fortunately, however, this is a rare complication.

On the other hand, in no case of acute rheumatic fever can we be quite certain that other pathological conditions may not occur which particularly on account of the great frequency with which they appear always renders it questionable whether they are to be looked upon as complications or as an integral constituent of the pathologic process. These are the **inflammatory changes in the endocardium of the left ventricle**, further those of the serous membranes, particularly the *pericardium* and the *pleura*, very rarely and probably only by a propagation from the pleura to the *peritoneum* and extraordinarily rarely to the meninges of the brain and spinal cord. The great rarity of meningitis favors the view that these complications are due to secondary infection, to embolic processes from the heart or due to other individual conditions.

Early, even in the first days of the disease, serious phenomena which point to implication of the organs of the chest may appear. The patient who is immovable on account of the inflammation of his joints now shows difficulties in respiration, often accompanied by pains in the cardiac region or by stitches in one or both sides of the chest. Respiration is rapid, superficial on account of the pains, insufficient breathing causes stasis of the blood in the veins of the neck, this gives rise to a swollen appearance of the face and to a bluish tinge in the color of the face.

The pulse, which up to now has been full and strong, the number of beats corresponding to the height of the fever, becomes more frequent, the artery is less filled, the tension slighter. Frequently the irregularity and unevenness of the cardiac contraction, with very irregular pulse, points to the development of a beginning *inflammation of the heart*. The entire heart, its external coverings, the pericardium, as well as the internal cover, the endo-

cardium, and the muscular layers lying between these, may, in severe cases, be implicated in the inflammatory process.

Frequently, however, the inflammation is limited to the endocardium, and particularly to the valves of the left heart, showing a preference for the *mitral valve*. A less severe endocarditis, not affecting the entire border of the valve or numerous chorda tendineæ, may also develop very insidiously without especial signs. On the other hand, an audible systolic murmur at the apex of the heart may also be due to other causes than imperfect closure of the inflamed valve, which would result in the regurgitation of blood into the auricle during the systole. The changed manner of the contraction of the heart muscle, under the influence of high fever, in those who have been previously anemic, may bring about a systolic murmur even with quite normal cardiac valves.

We may conclude with certainty that an endocardial disease of the valve is the cause of such a murmur if phenomena of regurgitation of the blood, and faulty flow from the right heart to the lungs, to the left auricle—increased cardiac dulness to the right, and increase of the second pulmonary sound—are added.

More rarely than the mitral, are the *semilunar valves* of the aorta the primary seat of an endocarditis; they are more rarely affected by a propagation of the inflammation from the large (anterior) leaflet of the mitral valve to the semilunar valve at the base. If plentiful thrombotic deposits occur so that the aorta becomes narrowed during the systole, a systolic murmur occurs over the origin of the aorta; if the closure of the aortic valve is implicated in any manner, by softening and pressure or by rupture of one or more leaflets, a diastolic murmur occurs. Then the natural consequences soon develop: Dilatation of the left ventricle, regurgitation to the lesser circulation and to the right heart. The pulse becomes a *pulsus celer*.

The soft thrombi which are deposited upon the diseased valve bring on a new danger in the affection: Their *loosening and the carrying of thrombotic particles* into the course of the arterial system. Clogging of smaller, and even of larger arterial twigs (embolism), may occur in this manner, in the spleen, kidneys, in the brain, in the heart muscle, etc. There are then formed, if the so-called terminal arteries are blocked, necroses of the tissues with inflammatory demarcation (embolic infarct), which in the heart, in the brain, in the wall of the aorta, bring especially serious consequences with them.

In this manner the original morbid picture of acute articular rheumatism may show manifold modifications.

It is assumed by some that **pericarditis**, which frequently appears in acute rheumatic fever, occurs in the manner just mentioned, i. e., by the carrying of thrombotic material from the primarily diseased cardiac valve into branches of the coronary arteries of the heart, therefore, occurring by way of embolism. This cannot be contradicted with complete certainty, as a valvular endocarditis which is able to furnish thrombotic material of this kind is liable to arise without producing symptoms, it may even for a time run an entirely latent course. But the not infrequent appearance of pericarditis, without subsequent phenomena which point to a pre-existing or continuing endocarditis, is in favor of the view that the cause of acute rheumatic fever, which is not known up

to this time, is in itself capable of affecting the pericardium without an intermediate endocarditis.

But no matter how the endocarditis may have occurred in the course of acute articular rheumatism, it may be easily recognized by constricting pains in the cardiac region, usually radiating to the left side of the neck and the left arm—pains which occasionally correspond to a very irregular cardiac activity at the onset of a pericarditis are exaggerated by a rhythmical, that is, arrhythmical, increase. Only, if the patient is in a comatose condition as the result of the severity of the previous affection, nothing will be noted regarding pain, and pericarditis must then be recognized by other signs; a failure to observe these may cause the pericarditis to remain latent.

The most objective signs of a pericarditis are:

1. The *pericardial friction sound* which may be observed by auscultation, as a soft, occasionally even as a sharp, scratching, a rubbing to and fro, being more or less perceptible and, occasionally, even felt by the patient himself. It first appears at the base of the heart, at the left border of the sternum, but, under some circumstances, according to the part of the pericardium first affected, at the xiphoid process or even at the apex of the heart. This pericardial friction sound is only partly synchronous with the cardiac sounds, it occurs between the pauses, more or less completely filling them, but it has no constant relation to the cardiac sounds. By this property it differs from an endocardial murmur, which in general may have the same acoustic properties.

2. *The signs of an effusion into the pericardium.*

As soon as a plentiful effusion of fluid is added to the roughened condition, due to inflammation of the pericardial surfaces, the surfaces which are covered by a shaggy fibrin layer are separated from each other, and if they no longer come together at the anterior surface of the heart the *friction sound disappears*. It may reappear again if the parietal pericardium is forced to the visceral pericardium by pressure upon the anterior thoracic wall, or the patient assumes such a position that, on account of the gravity of the organ, a portion of the anterior surface of the heart comes into contact with the anterior thoracic wall, and this again with the parietal pericardium.

The greater the amount of fluid that collects in the pericardium, and this often occurs very rapidly so that the increase may be followed from day to day, the accumulation in the pericardial sac can be determined by percussion, and the more obvious are the phenomena of the withdrawal of the heart from the thoracic wall. These consist in the *apex beat becoming faint and its complete disappearance and the diminution of the cardiac sounds*.

Increase of cardiac dulness as the result of effusions is first shown at the *base of the heart*, soon, however, dulness increases in a transverse direction and, finally, there appears a dull area of pyramidal shape with the apex above, the sides of the triangle diverging downward and outward so that often both nipples, at least the left, is included in the dull area.

Posteriorly upon the thorax, the filling of the pericardium with fluid can only be determined if it be very considerable. The heavy sac, with the heart, sinks downward to the left and compresses the lower lobe of the left lung, not infrequently to a sufficient degree to diminish the percussion notes and

the vesicular respiratory murmur, so that bronchial breathing appears in place of the latter.

In cases of severe rheumatic pericarditis, pleurisy is also simultaneously present, which shows itself by *pleuritic stitches and by pleuritic friction sounds*, further on, by dulness posteriorly below, unilaterally or bilaterally. Upon the left side, the area of dulness is higher than upon the right, because, as has been mentioned, there is added dulness due to compression of the lung by the pericardium filled with fluid. But even without pericardial effusion, there may be dulness upon the right side posteriorly, next to the vertebral column, in that, as W. Ewart assumes, the effusion of fluid into the pericardium forces the liver over, thus compressing the right lower lobe.

But other phenomena also occur besides the pain produced by the inflammation of the serous membrane of the chest and the increasing difficulty in respiration. The heart is markedly influenced in its activity by pressure of the fluid which accumulates in the pericardium, which increases to the extent that it reaches the limit of distention of the pericardium. The diastolic filling of the cavities of the heart, especially of the auricles, becomes more and more incomplete, the filling of the aortic system, as a result of this, is less and less sufficient, and the blood increases more and more in the right auricle. This is the reason of the cyanotic swollen appearance of such patients, and the frequently conspicuous filling of the veins of the neck, with their undulatory movements produced by respiration and cardiac movement. As a result of this circulatory disturbance, general dropsy may occur. The urinary secretion which has diminished from the onset becomes still more reduced on account of the fever and profuse sweating, the urine is dark, shows a sediment of urate salts, and often, as the result of blood stasis, contains albumin, even if this has not previously been present in consequence of the rheumatic affection.

As a special *complication*, in addition to the previously mentioned disturbances, *catarrhal* and *catarrhal pneumonic* changes may occur in the lungs. Formerly they were very much more frequent than they are now, with our present method of treatment, but special conditions, such as previous catarrhs, pulmonary emphysema, cardiac weakness the result of obesity, faulty nursing, may even now favor their appearance. It is obvious that such complications are an especially dangerous addition to the already very serious affection.

Patients that were previously weak, especially regarding the heart, the anemic, the very fat or those that suffer from fatty degeneration of the heart, may succumb in a few days from such a pericarditis. Upon the whole, however, a fatal termination, even in severe cases, is a rarity. As a rule, after a duration of several days of this very serious condition, the exudate in the pericardium begins to decrease obviously, the figure produced by percussion becomes smaller from day to day, and friction sounds begin to return at the base of the heart. To the same extent the heart and lungs again become free, the difficulty in respiration and the other phenomena decline, the appearance of the patient improves and the condition of the pulse increases, the daily amount of excreted urine rises.

If in the meantime the arthritic phenomena have diminished the patient slowly appears to enter upon convalescence. Only too frequently, however,

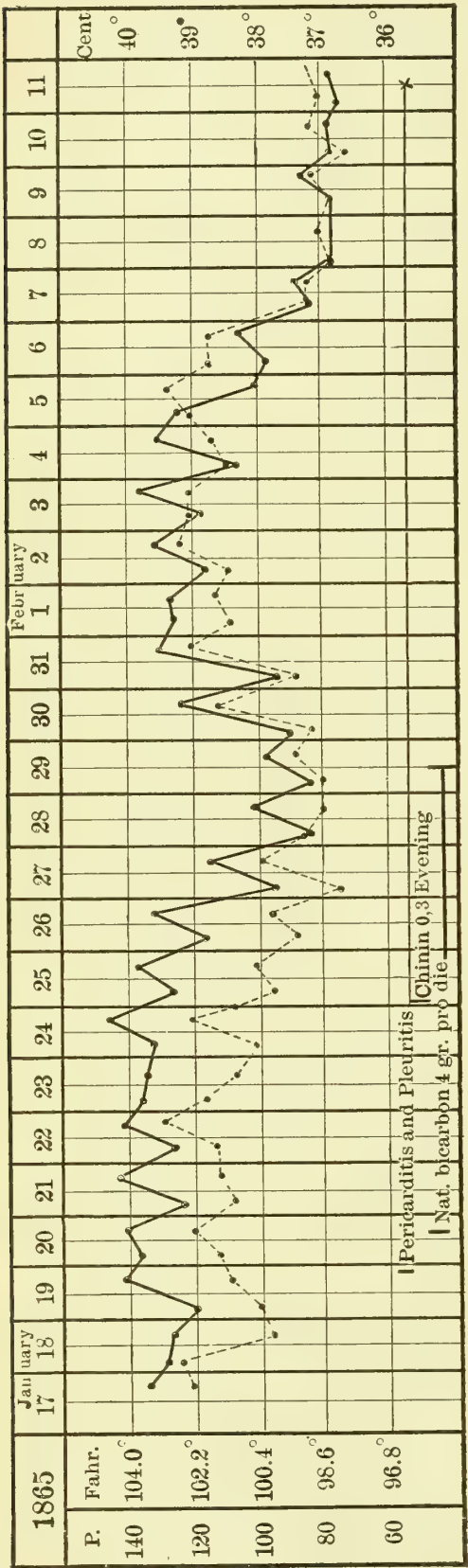
quite unexpectedly, *new arthritic swellings appear* after defervescence has begun by lysis. Again the temperature rises and this relapse may be a very serious condition in a patient who has been previously weakened.

Very often the course of acute articular rheumatism, because it is uninfluenced by an effectual medication, or because the latter is insufficient and has not been continued long enough, consists of a number of these relapses, in which at one time these, at another time those joints, and, occasionally, one and the same joint, may be affected several times. With this, it may be that inflammation of the heart and other severe complications only occur in one of the relapses. English and American physicians have called attention to a peculiarity of the disease which is quite rare in Germany, occurring especially in *children*, namely, that *small, hard, immovable nodules* appear over joints, tendons, fascia or bones, these often being noted during the decline of the disease.

The following is, in general, the course of the **temperature** curve in an attack of rheumatic fever: Rapid rise of the temperature at the onset, then a brief or longer continuous range, with moderately high exacerbations, rarely going above 104° F., with a retardation of the inflammation in the joints and other organs, a defervescence by lysis to almost normal; upon the appearance of new arthritic inflammations the temperature rises again and there is a repetition of the same temperature course of longer or shorter duration. Thus, the entire curve may consist of several divisions closely resembling one another.

The charts shown here will explain the previous remarks. The first (Fig. 42) shows a part of the febrile course in a case treated by me thirty-five years ago.

The patient, a strong man who eight years previously had an attack of acute articular rheumatism, entered the hospital in the second week after the onset of his disease. Upon admission, the heart was normal, but from January 18th on, pericarditis and pleurisy developed, the main signs of which could be determined for three weeks longer. The patient now appeared to have entered upon convalescence and after an interval of sixteen days in which he was



free from fever, fresh joint inflammations reappeared, the fever rising to 104° F. This relapse, in which pleurisy again appeared on the right side, lasted fourteen days; the fever fell in five days by lysis. In spite of the continued use of sodium bicarbonate, fever returned after three days, lasting six days, without new joint phenomena. Upon April 2d the patient was fully convalescent, and was discharged from the hospital without demonstrable signs of heart disease.

Charts 43 and 44 show the fever course in severe cases during their onset treated by salicylates. Both are especially instructive in so far as the influence of an interruption of the salicylate treatment, by substitution of sodium bicarbonate in one case, is plainly shown. Salicylate of sodium had to be discontinued on account of marked difficulties which it produced. Aspirin also caused vomiting in the patient whose chart (Fig. 43) is shown above, and therefore sodium salicylate in an effervescent form was tried. In this manner the drug was well borne. From November 30th to December 8th the patient was free from fever, upon December 8th the relapse occurred.

If the patient finally enters upon *convalescence* some difficulty remains for a longer or shorter time, particularly signs of general weakness, but, above all, a painful stiffness in the previously affected joints; if a faulty position has been assumed for some time *painful muscular contractions* occur or other phenomena on the part of the thoracic organs, conspicuous anemia and marked emaciation.

It is worthy of note that even in those cases in which all local phenomena have disappeared entirely, often for weeks afterward, even upon a uniform quiet condition of the patient, subfebrile temperatures appear in the form of slight evening exacerbations, for which no cause can be found. The general implication of a convalescent showing itself in the form of anemia and emaciation, in other febrile dis-

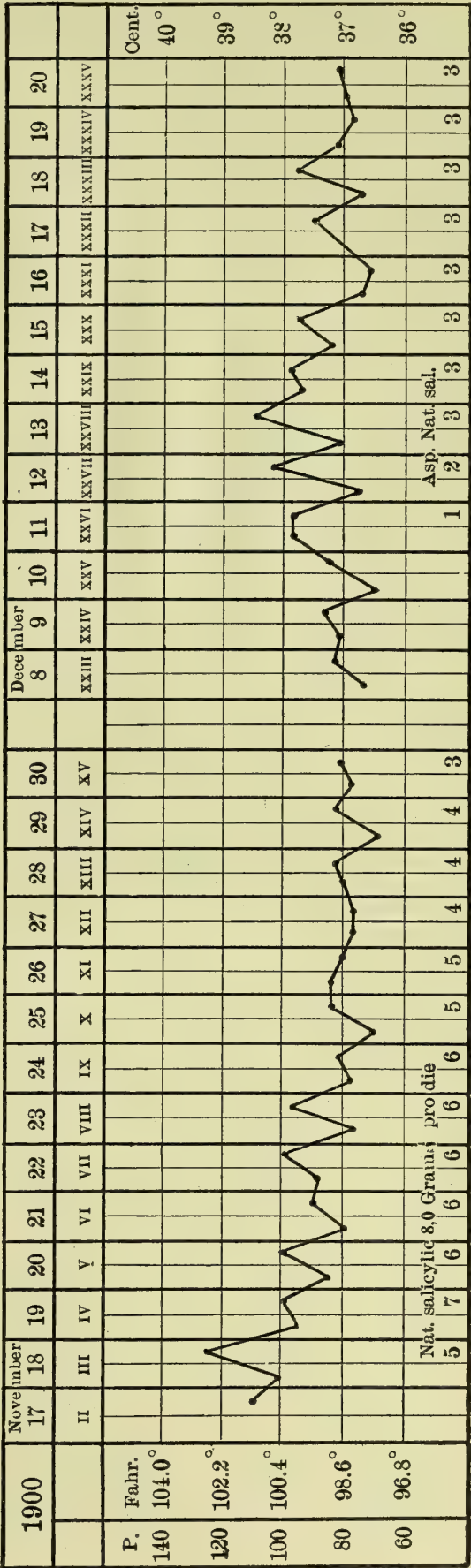
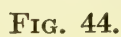


Fig. 43.

Such a severe clinical picture as I have described is rarely seen nowadays, because in most cases from the onset remedies are used which rapidly ameliorate the principal symptoms. The salicylate treatment has robbed the disease of much of its severity and immediate dangers, although it has not markedly diminished the frequency. Pericarditis with its consequences has become less noticeable with our present treatment, but endocarditis is common enough, whether actually as frequent as formerly, cannot be determined with certainty. But just this very common appearance of endocarditis, in spite of



There are cases in which endocarditis, and also pericarditis alone, appears as a severest phenomenon of the disease, and arthritic inflammation only occurs later on.

It might be thought that in a very slight intensity of the disease the causative agent would show its effect in only one joint, which would be especially predisposed and localize itself here, and that in this manner the disease

might characterize itself as a rheumatismus monoarticularis. But most frequently, mono-articular rheumatisms chiefly are characterized by a special severity and a prolonged course, and this makes it likely that in these cases, most often, we are not dealing with an acute or subacute articular rheumatism *but with an articular inflammation due to other causes*, among which tuberculosis, gonorrhea and syphilis should be first considered.

As a *sequel* or complication worthy of notice, *chorea* must be mentioned, which frequently occurs, either suddenly or insidiously, in older children after a mild attack of articular rheumatism. The connection between chorea and articular rheumatism may be of very various kinds, in some cases the connection which points to this may depend upon the presence of a murmur due to an endocarditis, which perhaps is only accidentally found if, upon the presence of the frequent chorea and an endocardial murmur, an examination of the heart is undertaken. Articular phenomena may be entirely absent in such cases and even remain absent. Without entering more minutely upon the connection of chorea and acute articular rheumatism and endocarditis, I shall only say that this is explained by embolic processes in certain parts of the brain, or also by the toxic action in connection with the assumed bacterial cause of articular rheumatism. The assumption that embolic processes may play a part in this has been brought forward because of the cases in which endocardial proliferations and thrombotic deposits have been found, post mortem, upon the valves of the heart.

I mentioned previously that cases occur in which the *first phenomenon* of the disease was endocarditis, the articular phenomena only occurring days afterward. Especially in children have such observations been frequently made. Such cases show great similarity to diseases of other kinds, in which only secondarily after a primary endocarditis, individual arthritic inflammations or attacks succeeding each other arise. These forms of endocarditis, however, are of a malignant nature, in so far as the course of the disease shows a tendency to necrosis, in which the great danger of repeated embolism in the arterial system arises. Usually, then, the character of the cardiac affection is in keeping with the embolic focal disease; therefore, in this manner, i. e., by carrying the inflammatory material from the heart, arthritic inflammations occur, which usually run their course with the production of pus in the joints, and in the most favorable case run a very long tiresome course, damaging the joints. There is found, therefore, in this malignant form of endocarditis, which is also designated as "ulcerative" endocarditis, the same conditions as in pyemia, only with the difference that in the latter the primary focus of the disease from which the metastasis arises first occurs in the course of the pulmonary artery, not in the heart, having its seat anywhere in the body, and that from this primary focus the entrance of inflammatory material first occurs in a contiguous vein.

The purely mechanical part of this process might also occur in case of acute articular rheumatism with preceding endocarditis, resembling septicopyemic morbid processes, to which also the ulcerative form of endocarditis belongs. But the nature of the process is a different one, *for the inflammations of acute articular rheumatism in the heart as well as in the joints, are characterized by their benign character*, their but slight tendency to pus formation, so that

if in a particular case a malignant course is assumed, the addition of something new, something special, therefore, a complication, must be assumed.

We know that certain **bacteria**, especially streptococci and staphylococci, are the causes of such inflammatory processes, that pyemic metastatic diseases arise by their entrance and distribution in the body. As has been mentioned, the latter occurs frequently from the focal area in which they have first collected. This may be at any part of the body in which an external injury has occurred, in many cases, however, a secondary focus or collection in the lung or in the heart forms the point of origin for further affections in the system. In the heart such secondary areas will form and be the point of origin for further dissemination if the valves of the heart have previously suffered from changes. Thus, it occurs that for days and for years an articular rheumatism that has left a valvular disease as the result of a non-determinable, so-called "cryptogenetic" infection, allows the appearance of an *ulcerative endocarditis* with all of its consequences, among others also of metastatic arthritic inflammations. In spite of the similarity which this clinical picture shows with acute articular rheumatism, it is not the same disease. The differentiation, however, is of great importance, especially on account of the prognosis, which in such a case is quite unfavorable.

Other clinical pictures which have certain symptoms in common with acute articular rheumatism may develop as the result of infection or be of cryptogenetic origin, in which, besides articular phenomena, all varieties of metastasis occur, *cutaneous inflammations* of a milder or severer kind (erythema multiforme, erythema nodosum, purpura hemorrhagica), with or without endocarditis. A form of purpura hemorrhagica has been especially described as *peliosis rheumatica*.

ETIOLOGY

It is, therefore, seen that acute articular rheumatism has much similarity and some connection to other diseases which certainly are due to *infections*, i. e., are produced by the entrance of bacteria into the body. Thus, the thought was quite natural that acute articular rheumatism also owed its origin to an infection, whereas, formerly, the disease was looked upon as a prototype of a malady produced by refrigeration. This view went so far that the designation "rheumatic" was used synonymously with "due to refrigeration." At first but very mildly, however, gradually with greater certainty, this older view was combated. Now no one any longer doubts *that in the case of acute articular rheumatism we are dealing with an acute infectious disease* and that refrigeration only plays the rôle of an important *predisposing* factor. For years we have been engaged in the attempt to find the specific cause of the disease.

As previously mentioned, it has been particularly the connection of acute articular rheumatism with acute infectious diseases and the general tendency which etiologic investigation has adopted in the last forty years, that have gradually brought about this change in opinion. With this, many previously observed phenomena that were now investigated with greater attention, were viewed in an entirely new light and could be utilized as a decided support for the new opinion. Thus, the occasional *locally increased appearance* of acute

articular rheumatism, and *the appearance of the same after local diseases* were without doubt due to infection. This factor is not only of great importance etiologically in the case of acute articular rheumatism, but is also valuable as regards prophylaxis. American and English physicians for a long time had already called attention to the frequent occurrence of acute articular rheumatism *after an attack of tonsillar angina*. Lately, also in Germany, this condition has been more and more noted and the frequency of this appearance could be confirmed.

For a long time the multiple arthritic inflammations have been known which occur in the course or at the onset of convalescence of *scarlatina*, arising with or without endocarditis. This "scarlatinal rheumatism," not, however, the malignant pyemic arthritic inflammation which is occasionally the result of *scarlatina*, has the greatest similarity with ordinary acute articular rheumatism, in so far that it may also be caused to disappear rapidly by treatment with the salicylates. Also in various other diseases, especially in such that run their course with pyogenic processes, such as dysentery, bronchiectatic cavities, these conditions which have been designated "rheumatoid" by C. Gerhardt, have been observed.

The endeavors to discover a *specific pathogenic agent* in acute articular rheumatism has as yet not been decided with definiteness. Different bacteria have been found in the cadaver, especially in the endocardial proliferations, in the synovial membranes of inflamed joints, in the living body only in very rare cases in the blood, very rarely in the synovial fluid and, finally, also by G. Singer in the voided urine, examined after taking all precautions. In the greatest majority of cases cocci were found, especially *staphylococcus albus* and *citreus*, by some French authors bacilli were also found. To those that desire to investigate the present standing of the bacteriology of acute articular rheumatism, I must refer to a book recently published by H. Triboulet and A. Coyon.¹

The comparatively benign character of the inflammations in acute articular rheumatism, compared to those changes which are produced by the previously mentioned cocci, which usually run their course by producing pus, permitted the view that in acute articular rheumatism the affection depended upon the action of *bacteria with an attenuated virulence*. However, according to this view, acute articular rheumatism would belong *to the group of septic diseases, but it would represent a benign form of the same*.

That the condition is due to a bacterial affection is, therefore, very probable, even if the strict proof of this assertion is not yet at hand. Especially the frequent appearance of the affection in connection with an angina, in which various bacteria play a prominent rôle, appears to support this view. The diseased tonsils would, therefore, represent the port of entrance for the virus, which then, as in septic diseases, would increase in the blood and here and there in the organism, according to the predisposition of individual areas or tissues, produce inflammatory processes. But similar to the oral and pharyngeal cavity, any other part of the body that is in connection with the external air, also the intestines, the urogenital apparatus, might form

¹ Le rhum. art. aigu. Paris, 1900.

the port of entrance for the virus. The simultaneous appearance of the inflammation of many joints would point to the fact that for a longer period numerous quantities of bacteria had been circulating in the blood stream, and had reached the synovial membranes of the joints and been deposited there, whereas in other forms of articular inflammation, which ought to be looked upon as metastatic, as in pyemia, gonorrhea, etc., in which at the time only one or a few joints are affected, these inflammations would be due to a *sudden* immigration of the bacteria from a primary bacterial focus to the joint in question.

The appearance of a multiple joint inflammation, by attacks in the course of acute articular rheumatism, the frequent relapses in the disease, after they have apparently run their course might be explained in an analogous manner to that of other bacterial infections, that either from a focus of accumulation, in which, above all, an increase of the bacteria occurs, a transference into the circulation takes place from time to time, or also that gradually in the course of the disease, by the production of bactericidal or of so-called antibodies, the pathogenic agent and its direct action becomes weakened and destroyed, that, however, the combat between these various forces remains undecided for some time, first favoring one and then the other, before a conclusion is reached.

It might be believed that the decisive action of salicylic acid is one of the most certain proofs of the infectious nature of acute articular rheumatism. Salicylic acid is certainly a very active antiseptic, sodium salicylate, however—and this remedy is now almost exclusively employed on account of the irritative action of salicylic acid upon the mucous membrane of the stomach—has but very slight antiseptic action. Its effectiveness, therefore, must depend upon other than upon antibacterial action.

Even though the *actual cause* of acute articular rheumatism is not yet sufficiently known to us, still we recognize quite a number of *predisposing causes*. Among these, *refrigerations* of the most various kinds certainly play a most important part. This is favored by the circumstance that the disease which is distributed over the entire earth occurs with special frequency in such countries and districts in which refrigeration, as the result of climatic conditions, occurs especially readily, as for example in Great Britain, and in these countries the seasons in which chilling occurs most frequently are especially causative, therefore, winter and spring. Here in Freiburg the admissions in the fifteen years from 1877 to 1891, in which the cases of rheumatism showed a proportion of 3.2 per cent. of all cases admitted, the maximum of frequency occurred in April.¹ In the local distribution, as well as in the distribution according to season, an *epidemic increase of frequency*, even limited to localized areas, even to *individual dwellings*, may occur, and that the most varied meteorological factors may have an influence only requires to be mentioned. Nothing positive in this respect has as yet been determined.

In regard to the *individual predisposition*, heredity plays a certain rôle, but a much greater part is played by age. Acute articular rheumatism is

¹ Compare the dissertation by Dr. James Hugo, Statistisches und Klinisches über acuten Gelenkrheumatismus, 1893.

particularly a disease of adolescents; in the greatest majority of cases the first attack takes place some time between the fifteenth and twenty-fifth years of age. In early youth, up to the fifteenth year, girls are more frequently attacked than boys. The disease also occurs in early infancy, although more rarely.

A special predisposition is shown by pale, chlorotic individuals, in those that have a tendency to tonsillar angina.

An increased predisposition remains after an attack of articular rheumatism, also in cases in which no cardiac change has taken place. It is possible that other joint diseases, even after they have disappeared, may convey an increased local predisposition to acute articular rheumatism. In many cases of gout, not only does this local predisposition, but the anomaly of metabolism which goes hand in hand with this disease, appear to have a certain tendency to acute articular rheumatism, so that mixed forms between articular rheumatism and true gout occur.

DIAGNOSIS

We now come to consider the *diagnosis* of acute articular rheumatism. As was previously mentioned, there are many morbid conditions which, with a very lax use of language, are designated as "rheumatic," which under some circumstances may occur acutely but which most frequently are due to entirely different conditions from those of acute articular rheumatism. This condition should only be diagnosticated if a *multiple* articular joint inflammation occurs in a subacute or acute manner, after a marked refrigeration, or perhaps an inflammation of the throat has preceded for a short time, also if there be great tendency to sweating, early phenomena on the part of the heart appear, and upon treatment by the salicylates a rapid retardation of the symptoms occurs. A previous attack of articular rheumatism would support the diagnosis. But it is self-evident that any one that has had one or more attacks of acute articular rheumatism may later on acquire another variety of acute articular inflammation.

There are, however, quite a number of arthritic inflammations which begin *acutely* or *subacutely*, which, on account of their chief symptoms, especially the arthritic inflammation and the fever, may present the greatest similarity to acute articular rheumatism. *Gonorrheal* arthritis belongs particularly to this category, in which several joints may be simultaneously affected, and then it runs its course with high fever. If in a certain case the salicylate treatment is inefficient, it must be determined, above all, whether gonorrhea has preceded or whether it still exists. The tendency to an implication on the part of the heart is slight, but it occurs. The course of gonorrheal arthritis is quite different from that in acute articular rheumatism, it fastens itself upon individual joints and very frequently connective tissue adhesions occur in the joint. In *septicopyemic* arthritis in which usually only one joint is affected at a time, the other phenomena of septicopyemia are so well developed, as a rule, that arthritis occurring in their course may be readily referred to it. If these are absent and a primary focus of affection cannot be determined, as in the case of so-called cryptogenetic sepsis, and if several joints are affected, the diagnosis may remain doubtful for several days.

Occasionally another disease which belongs to this category may temporarily resemble a beginning acute articular rheumatism, the following case history will show this: A boy aged fifteen was admitted to our wards in the spring of 1899. Four days prior to his admission he was attacked by pain in both feet, there was swelling and redness in both ankles, high fever was present. Prior to his admission to the hospital, salicylate of sodium was administered, which could still be recognized in the urine, but the pains did not ameliorate; upon admission both lower legs and the joints of the feet were markedly swollen and reddened, some albumin was present in the urine; the heart negative, the spleen slightly enlarged, the temperature 103.4° F. The next day fluctuation could be determined over one of the tibia; it was soon evident that this was a case of *osteomyelitis*, and the patient was at once sent to the surgical division. The left tibia was opened and various pus foci were exposed in the bone, in the right tibia only one abscess was opened. In the pus from the foci in the bone, staphylococci were found, the patient had to remain in the surgical department for many months.

If, as in this case, exceptionally the simultaneous affection of several extremities by osteomyelitis occurs, and if, as frequently happens, cardiac phenomena, especially pericarditis, are present, the differentiation from acute articular rheumatism will depend upon the determination of whether the joints are actually the seat of inflammation, and whether the localization of the same is not more in favor of an inflammation in the skin covering the bone than in the bone itself.

In cases in which there is the slightest suspicion of *syphilis*, in which there is otherwise similarity to acute articular rheumatism, the periosteal inflammation, especially prominences in the bone in the region of the joint, acquire great significance. The diagnosis that we are dealing with a *syphilitic* periostitis depends naturally upon other characteristic signs of syphilis. It is worthy of note that in the florid stage of syphilis, especially in the cases in which the eruption runs its course with fever, a form of multiple arthritis may occur which shows the greatest similarity to acute articular rheumatism. In such a case the lack of result from a treatment by salicylates and the rapid improvement of the joint phenomena and of the fever by the administration of mercury, and by the combined treatment of mercury and potassium iodid would be determining in the diagnosis.

In many cases, especially in youthful individuals and in the first attack, true *gout*, *arthritis urica*, if it does not, as is usual, limit itself to the *metacarpo-phalangeal* articulation of the *great toe*, but affects several joints, it may resemble acute articular rheumatism, but in this instance, as a rule, the acute inflammatory phenomena in the affected articulation, the redness of the skin and the pain, are much greater than in acute articular rheumatism. The courses are so far different that, as a rule, as far as the inflammation goes, it is limited to the joints first attacked. Above all, in the diagnosis the proof is important of those etiological conditions which are determining of gout, especially heredity, chronic alcoholism and chronic lead poisoning.

Articular rheumatism occurring subacutely in its onset cannot be readily differentiated from a form of *very chronic multiple arthritis* which occurs in younger or older individuals, especially in females, as a result of damp

clothes, insufficient nutrition, sorrow, care and other emotional conditions, but, occasionally, without any assignable cause, most probably in the majority of cases due to some infection as yet not recognized, and which has received the improper name of "arthritis pauperum," principally probably in contrast to arthritis urica which occurs in those accustomed to high living. In this disease, on account of the nodular swelling of the finger and other joints, the affection has also been called "rheumatismus nodosus," which causes multiple changes, giving rise to gradual disappearance of cartilage or connective tissue, or change of the same to adhesions, or other changes in the joints, and belongs to the group of "*arthritis deformans*," but, in spite of numerous joints being affected, which are often quite painful, no fever or only very slight transitory fever is present, and, in spite of its existence for years, the *endocardium* is not affected. In this disease, *salicylic acid* is, as a rule, quite valueless, and at most the pains may be only slightly lessened by it.

Some affections belonging to the group of deforming articular inflammation may be designated as chronic articular rheumatism, in so far as previously the affected patients may have recovered from one or more attacks of acute or subacute articular rheumatism. But it is most probable that, in order to impress gradually upon the disease this deforming character, still other causes, particularly of an infectious or infectious-toxic nature must be added. The previous attack of acute articular rheumatism or several acute relapses could only, therefore, be looked upon as predisposing causes. It is not in the nature of acute articular rheumatism that the arthritic inflammations which belong to it bring about profound alteration of the tissues in the joints, even in a prolonged course of the disease. After the characteristic peculiarities of the disease have been described, we are able to differentiate them from acute, that is to say, subacute articular rheumatism, which is of great importance in prognosis.

PROGNOSIS

The *prognosis* in acute articular rheumatism, especially in regard to the acute inflammation, as also in regard to the danger to life, is favorable. Upon early and proper treatment and sufficient after-treatment, as a rule, all phenomena on the part of the joints and their surroundings disappear completely.

The principal danger to life in the individual case also to the future health, consists in the implication of the heart. For this reason, from the onset, the prognosis is doubtful in every case.

The mortality which is *immediately* due to articular rheumatism is very slight. Reports vary between 1.3 per cent. and 3.6 per cent. of all those attacked. Besides the hyperpyrexia, which in the majority of cases must be attributed to the causative agent of the disease, all causes of death belong to the realm of complications or to certain individual predisposing affections which are dangerous to life in every febrile affection (obesity, especially predisposition to pulmonary complications, etc.). In cases that terminate fatally, the *post mortem findings*, therefore, show principally such changes as are not directly in combination with the actual disease. Only those fresh changes found in the heart usually belong to the rheumatism itself. In the joints,

besides the somewhat increased, somewhat turbid, and occasionally somewhat hemorrhagic synovial fluid, as a rule, there is only a more marked hyperemia in the three folds of the synovial membranes. The marked injection of the synovial membranes which was certainly present in life, disappears in death as does other arterial hyperemia.

In the *individual case* the prognosis is rendered unfavorable if early or later phenomena occur which show the implication of the heart in any form. Less unfavorable are changes in the mitral than in the aortic valves. The prognosis becomes doubtful even in regard to the maintenance of life, if during the decline of the disease pericarditis occurs. Obese persons or those previously weakened, especially those suffering from renal disease, are especially endangered. In those previously healthy, even in those that have retained a valvular affection from a previous attack, pericarditis even with severe phenomena, with a plentiful exudate, in the great majority of cases runs a favorable course, but even in these cases the dangers remain for life, and sooner or later result in circulatory changes which may shorten life.

It may be looked upon as a *prognostic important* peculiarity of acute articular rheumatism that the inflammations which occur in the joints, as well as those in the serous membranes, *exceedingly rarely lead to suppuration*. In cases in which this occurs a complication may be assumed, i. e., a simultaneous infection or one by pyogenic agents occurring in the course of the disease. Inflammations that are decidedly of long duration in individual joints or that have resulted from prolonged immobility, giving rise to disturbances of motion, which have their seats in the joints, tendons and muscles, are susceptible to improvement, and even complete cure, although only after a prolonged and careful course of treatment.

All complications, whether they be due to the constitution of the patient (obesity, diabetes, arteriosclerosis, anemia) or are the result of improper nursing (bed-sores, hypostatic pneumonia, sepsis, originating from the oral or pharyngeal cavities), render the prognosis unfavorable. The prognosis becomes very unfavorable if *hyperpyrexia* develops, with or without prodromes, although in these cases, even with severe cardiac inflammation, it has been possible several times to bring about the normal regulation of heat by *energetic cooling*, and by this means to maintain life.

THERAPY

The *treatment* of a case of articular rheumatism, as I have already indicated, is a more hopeful task than it was a quarter of a century ago. In the *salicylates* and in a number of other similarly acting substances produced by modern chemistry, such as antipyrin, phenacetin, antifebrin, salophen and others, we possess remedies which to a certain degree act in a specific manner upon the disease. Not in the sense that antiseptic or antitoxic actions destroy the cause of the disease or render it harmless. This is very unlikely, for, as we have already said, sodium salicylate, which is so very active, can scarcely be looked upon as an antiseptic. How its action occurs, upon what it depends, has not been determined.

In the same year in which salicylic acid was first used in acute articular rheumatism (1876), an English physician, Maclagan, believing that acute

articular rheumatism was a "miasmatic" disease similar to malaria, employed *salicin*, which was previously employed in malaria with decidedly good results. Salicin was decomposed in the body into saligenin and salicylic acid, and, therefore, owes its efficacy to these split products. For a time salicin was used in cases in which sodium salicylate was not well borne, lately, however, more effective remedies have taken its place (antipyrin, antifebrin, phenacetin, etc.).

Formerly the treatment of acute articular rheumatism consisted in measures which were frequently used to an extravagant degree to act against the refrigeration, and to prevent the patient from taking fresh cold. The patient was covered with wool; drinks and remedies that provoked perspiration were administered and, if high fever was present, remedies that had a cooling action, such as potassium nitrate were given. Still earlier, and up to the middle of the nineteenth century, the entire antiphlogistic apparatus was employed, and Bouillaud especially advised venesection "Coup sur coup."

A great advance in the treatment occurred as, owing to an observation of the acid condition of the sweat, the theory developed that the disease was due to abnormal acid production—lactic acid was supposed to be the cause—and *alkalies* in large doses were employed. Especially in England, where, as I have previously mentioned, the disease occurs with particular frequency, alkalines were systematically administered, especially potassium carbonate and potassium acetate in combination with quinin, as advised by Garrod. Under the influence of this treatment the urine soon became alkaline, and, as a rule, the joint phenomena and the fever improved. None of these methods of treatment can compare in the slightest degree in results with the **salicylate treatment**.

This is best employed in the following manner: As rapidly as is possible without danger, a certain saturation of the body with the preparation is brought about. The remedy should be administered at regular intervals day and night, carefully observing unfavorable actions of the remedy, such as vomiting, very marked tinnitus aurium, delirium. In our hospital we give, as a rule, every two or three hours $7\frac{1}{2}$ grains of sodium salicylate, a smaller dose to children in proportion to their age, and if a very high fever is present, on account of its accompanying symptoms, such as headache, difficulty in respiration, unrest, which disturb the patient a great deal, we double the individual dose during the afternoon. *The patient is not to be awakened from his sleep* to have the medicine administered, so that during the night one or two doses may be omitted. In this manner in twenty-four hours the patient takes from 90 to 120 grains of sodium salicylate, with this some tinnitus aurium and some difficulty in hearing appear but they disappear as soon as the dose is diminished. This may often occur after from three to four days if sufficient amounts of the remedy are given from the onset.

We usually give sodium salicylate dissolved in water; an addition of the juice of licorice, which disguises the taste of the sodium salicylate, is frequently more unpleasant to the patients than the drug itself.

With this dose, vomiting rarely occurs; should it occur, or the drug be disagreeable to the patient on account of its sweet burning taste, sodium salicylate may be administered in a powder or a capsule, some carbonated

water being given afterward, or it may be given in an effervescent mixture, so that with 0.5 sodium salicylate there is mixed 0.25 sodium bicarbonate, and to this solution in water, fresh lemon juice is added; a larger dose may also be given in watery solution per rectum.

Somewhat slower acting, but for this reason less useful, salicylic preparations are malakin, 1.0 per dose, and aspirin, 0.5 to 1.0 per dose. These are readily retained by the stomach.

Antipyrin in doses of 0.25 to 0.5, *phenacetin* 0.5, *antifebrin*, 0.2 every three to four hours, as well as some of the newer "antineuralgics" have also been employed in acute articular rheumatism, but they are not better than the salicylate preparations. Antipyrin in long use is not powerless in its action on the heart; antifebrin must be stopped at once if cyanosis appears.

Sodium salicylate is given in carefully diminishing doses when the phenomena improve, up to the time at which the inflammatory joint phenomena and the fever have disappeared entirely. Upon an increase of the phenomena or with an insufficient action of the early administrations the dose must be carefully increased. In our clinic we noticed a few cases in which for several days 150, even 160 grains had to be given in twenty-four hours. In contrast to other communications, I desire to remark that with the employment of sodium salicylate in acute articular rheumatism, we have never seen albuminuria which could be referred to the action of the remedy.

The *heart* must be carefully watched. Good nursing and a consecutive salicylic treatment are the only known remedies that will prevent endo- or pericarditis. If the signs of an implication of the endocardium or pericardium appear (irregular cardiac action, inflammation of the pericardium, or endocardial murmurs), an ice-bag or a Leiter coil is placed over the cardiac region; with severe pain or oppression, morphia hypodermically, 0.005 to 0.01, will ameliorate the condition. Pleuritic pains not yielding to cold compresses (Priessnitz) must be combated with morphia.

Very rarely do such large exudates occur in the pleural cavity or in the pericardium, threatening life so that aspiration must be performed.

The *inflamed joints* require, above all, a comfortable position of the affected limbs, enveloping them in cotton if there be great tension of the skin; rubbing with oil is valuable. Oil of chloroform (10 per cent.) may be used for this purpose. The late method of treating the inflamed joints with salicylic salves, especially with methyl salicylate (oil of gaultheria), which is readily absorbed and evaporates, this being rubbed into the joints and covered with gutta-percha paper so that it is air-tight, often becomes unpleasant to the patient and more so to those about him, by the strong, even if not disagreeable, smell of the same, nor does it actually show any marked results. Ice treatment of the affected joints is not advisable on account of the localization of the affection in numerous joints and also on account of the discomfort to the patient. On the other hand, in marked inflammation of individual joints and great pain, the ice-bag is useful. Great caution must be observed in its use. In a very severe joint affection complete immobility of the affected joint in a splint, or, under some circumstances, for example, in especially severe inflammation of a hip or knee joint, slight suspension and extension may be employed.

There is never occasion for puncturing and washing out of the larger joints with antiseptic fluids in acute rheumatic fever. In cases in which such a severe joint affection with a plentiful exudate occurs we are dealing with a gonorrheal or septico-purulent joint inflammation.

If the inflammatory phenomena in the individual joint appear unyielding, a plaster of cantharides may occasionally be very useful applied to or around the joints. The systematic employment of cantharidal plaster upon every affected joint, which was advised by H. Davies about 1860, which in many cases acts decidedly favorably although occasionally kidney affection appears later owing to the absorption of the cantharides, has been entirely replaced by the much more active salicylic treatment.

As in the case of every other severe disease, nursing and care of the patient is one of the most important constituents of the treatment. A uniformly warm room, sufficient ventilation, avoiding sudden drafts or sudden cooling the patient, are important. In a disease in which the patient is so immovable, a comfortable mattress and the avoidance of any local pressure must be carefully looked after. A heavy, fat patient should at once be placed upon a water bed, with a woolen comfortable over it, to avoid bed-sores. Where another bed can be utilized this should be employed so that the patient may daily, with great care (warmed sheets!), be moved into the other bed that the first bed may be freshened.

The *nutrition* should suit the condition of the patient, especially should it be adapted to the fever. With high fever, only fluid nourishment: milk, soups with or without eggs, rice, grits, tapioca should be given; with this, cooked fruit would be best. Coffee or any other fluid taken at breakfast may also be allowed, except if cardiac affections are present, then the action of coffee or tea upon the heart must be considered. If there is only moderate fever, there is some appetite, and the wishes of the patient regarding bread, meat and fish may be considered, naturally, with regard to the digestibility of the different substances.

The *plentiful administration of pure water* or of the mild alkaline mineral waters is very important on account of the great loss of water by sweating.

Scrupulous care of the mouth is not to be neglected, especially in patients who, on account of the formation of the mouth or on account of insufficient passability of the nose, breathe with an open mouth particularly in sleep. It should always be remembered in febrile diseases of all kinds that if *mouth-breathing* is prominent severe complications may occur by a dryness of the mucous membranes of the mouth and pharynx, anginas of various kinds, otitis media, parotitis, edema of the glottis, bronchitis and bronchopneumonia, and even general sepsis may occur.

Regulating the function of the bowels which, on account of the absolute rest, the marked sweating and the diminished intake of nourishment, is very easily disturbed, requires attention. Dietetic measures are useful if constipation is present, even mild laxatives, such as: Carlsbad salt, compound licorice powder, Apenta water, given in the morning, or the use of cascara sagrada in the evening; glycerin suppositories or an injection of water may also prove efficient. Diarrhea requires the use of opium, under some circumstances this should be preceded by a dose of castor oil.

Hyperpyrexia requires the most energetic use of external cold by baths, ice-rubbings, etc. Wilson Fox, in two cases complicated by endocarditis and pericarditis, in which the temperature had risen to 110° F. and 107° F., respectively, succeeded in saving the patients.

Convalescents require greater care than after most other diseases. Above all, it is necessary that the heart, which has been more or less affected, should be allowed to recuperate completely, particularly if a valvular lesion has resulted. The effect of being out of bed, the movements of the body upon the pulse, must be carefully controlled during the first period. Even slight bodily exertions must be avoided entirely for weeks.

The question often becomes very difficult, whether an endocarditis which has occurred during the disease still exists or whether the continuous audible cardiac murmur is the expression of a valvular lesion that has developed as the result of endocarditis. In this condition the great variation of the cardiac activity, precordial pains and rises of temperature may be looked upon as determining.

Where the circumstances of the patient allow, a rest in the country in a region that is well protected markedly assists convalescence.

Soon after the appearance of convalescence, carefully chosen hydrotherapeutic measures may be begun so that the skin and the entire process of metabolism is influenced. Luke-warm baths in the beginning, even early cool or cold sponging in the morning in well advanced or in strong convalescents, are of value. These are to be given at first in bed, later out of bed, the patient then, however, is to return to bed until he is warm again; later cool half-baths with friction and affusions with the bathing water are very active remedies to harden the patient and to prevent a return of the disease, to which there is a great tendency in many who have gone through an attack of acute articular rheumatism. These hardening processes are to be continued by the individual in question in his entire future.

Special methods of treatment are sometimes required by the changes that have remained in the joints, which, if they have remained from an attack of acute articular rheumatism and grow worse from time to time, are finally designated as chronic rheumatism. In such cases systematic bath treatment at home or at bathing resorts may be employed (Wildbad, Ragatz, Gastein, Baden Baden, Wiesbaden, Aachen, Nauheim, etc.). In choosing the proper place other indications must also be regarded (a high altitude, the simultaneous use of a saline or iron water).

Besides these measures, various mechanico-therapeutic remedies (massage, gymnastics, machine gymnastics) or electricity may be employed to remove stiffness of the joints, contractures, wasting of muscles, etc.

Only in very rare cases which are always due to complications or mixed infections do such severe arthritic complications occur in the individual joints that surgical or orthopedic assistance becomes necessary.

SEPSIS

BY TH. v. JÜRGENSEN, TÜBINGEN

THE time is not long past in which it would have been looked upon as remarkable had an exponent of clinical medicine written upon septic infection. This belonged to the domains of gynecology and surgery; to these specialties puerperal fever and wound infection were relegated. Now these diseases appear less and less, we have learned how to prevent them. To no small extent this is due to the fact that we have recognized what causes them. These affections are produced by *microorganisms from the great group of the schizomycetes*; in particular the chain-cocci (streptococci) and the grape-like cocci (staphylococci) in their different varieties and, according to their effect upon man, they are designated by the collective term of the **pyogenic cocci**.

We had succeeded in determining the cause of wound infection, by culture tests and by experiments upon animals, and then the question arose whether it was not likely that other morbid disturbances were caused by them. And this had to be answered in the affirmative. It was primarily shown that these microbes were present in all change in tissue which went hand in hand with suppuration, and, further, that when inoculated in pure culture they were able to produce these alterations. And more, a number of diseases which were strictly separated in our system of classification, fall within the realm of those produced by pyogenic microorganisms, such as osteomyelitis, erysipelas and endocarditis.

It is true, *differences were recognized in these so closely related pathogenic microorganisms*: The *grape-like cocci* form more circumscribed foci, they primarily produce tissue necrosis, to which a demarcating suppuration is added; the *chain-cocci* distribute themselves to the surrounding tissue and are primarily inflammatory in their action. Nevertheless, a reason for an absolute separation is not apparent.

Both may cause a constitutional affection by their products of metabolism, both, entering the circulating blood and becoming distributed in this manner, are even capable of collecting in all parts of the body and of producing new morbid foci. To this must be added that the grape-like cocci and chain-cocci are very often found side by side in the same organism.

The old designations: *Pyemia*, when purulent collections occur in several regions of the body, produced by thrombi which have been carried there; *septicemia* when these are absent and the damage to the entire organism is prominent; *septicopyemia* when both conditions occur simultaneously have now only historical value.

In point of fact, these divisions are but rarely enough justified, the designation *septic infection* or simply *sepsis* is more proper.

Experience teaches that certain *local* diseases, at least in great part, per-

haps exclusively, in the individual case, are due to staphylococci and streptococci, erysipelas to the latter, furunculosis to the former. But from the *general phenomena* of the fully developed clinical picture no conclusion can be drawn regarding the causative agent. And this is not of especial importance in practice. It would only become important if the pyogenic agents that have entered might be combated by protective substances, and it could be shown that these would have to vary for the different organisms. But we do not as yet recognize any difference regarding protection no matter what condition is present. Our indication consists in destroying the pyogenic organism, or, if this is not possible, in placing them in a position in which their property of life is greatly diminished and in which they are prevented from multiplying to a great extent, thus inhibiting their action.

Instead of the necessary preliminary question, "*Whence do they come, where are they found?*" the following, "*Where are they not found?*" would seem more appropriate, for they are met with everywhere; thus with great regularity upon the mucous membranes and upon the external skin. That these tissues, when entire and undamaged, form a powerful, protective wall is unquestioned; that any damage no matter how slight facilitates immigration is no less true. Slight desquamation anywhere upon the widely distributed surfaces of the covering membranes is nearly always present. But this is not absolutely necessary in every case. This has been proven by Garré's experiments upon himself. "He applied the entire mass of a pure culture of the staphylococcus aureus in the form of a salve upon the *healthy undamaged skin* of his left forearm, and four days later there developed an enormous typical carbuncle, the periphery of which was surrounded by a circle of isolated furuncles. The process lasted for several weeks, no less than seventeen scars remaining. From the morbid foci the yellow pus coccus could be obtained in pure culture. More positive results than those of Garré's experiments, which show the property of producing paronychia and furunculosis, could scarcely be shown by the specific-pathogenic property of pathogenic microorganisms in general. Small wounds of the skin are required by the eminently infectious anthrax bacilli to enter from the skin into the tissues; from Garré's experiment, we note that not even a minimal injury to the cutaneous coverings is necessary to make it possible for the pyogenic grape-cocci to unfold their specific pathogenic activity.

"Apparently, in Garré's experiment, they entered the skin from the pre-formed glandular openings; they first found their way into the depths of the cutaneous glands; by the power of their proliferation they produced necrosis of the latter and then invaded the cutaneous and subcutaneous connective tissue, accumulated themselves around the necrotic cutaneous glands producing a demarcating suppuration which led to elimination of the gangrenous cocci-containing tissue plugs, finally leading to cure by the production of scar formation."

On account of the importance of the case, I have quoted the report and the explanation of one of our first bacteriologists¹ literally.

¹ v. Baumgarten, Lehrbuch der pathologischen Mykologie. I, p. 303, Braunschweig, Harold Bruhn, 1890.

Wounds, whether they be of the external coverings or the mucous membrane of the uterus, which is laid bare in parturition, will form the *usual ports of entrance*.

By the investigations of Ph. Stöhr,¹ we know that in the healthy human being another road is open: that of the upper surface of the tonsils and the glands of the tongue. Their epithelium is forced aside, even partly destroyed by the constantly emigrating leukocytes in great numbers, and thus openings are developed which make it possible for the pus cocci to find entrance. Experience teaches *that, in fact, an angina (tonsillitis) introduces sepsis*. In cases like the following it becomes extremely probable that angina was the *first, local disease*.

OBSERVATION I

Phlegmonous angina. Malignant edema of the left half of the chest. Purulent inflammation of the pleura and mediastinum, surrounding the pneumogastric and the phrenic nerves. Further development of the malignant edema over the surface of the body, septic eruption with vesicle formation. Severe general symptoms, especially also of the central organs. Death.

Infection by *streptococci* and *staphylococci* (original observation).

Woman aged forty-three, upon the afternoon of February 4, 1886, suddenly taken ill with marked chills followed by high fever. An angina develops, accompanied by swelling of the glands of the neck, which, however, does not go on to the stage of supuration. The symptoms of which she complained lessened on February 6th, whereas the fever continued. Upon the evening of this day I saw this lady who was well known to me.

Mild cerebral symptoms, showing themselves by active delirium and alteration of the posture of the patient, scarcely noticeable to the persons about the patient. *Circumscribed edema and erythema of the left cheek*, nothing abnormal to be seen upon the neck. *But from the left clavicle downward to the second rib distinct doughy edema*, externally reaching to the shoulder, somewhat painful upon pressure. *Painfulness of the shoulder joint* from the sulcus bicipitis and from the axilla, as well as of the *two first ribs* at the sternal border. *Spleen* distinctly enlarged, lungs and heart normal.

Upon the morning of February 7th: *To the right of the sternum* between the third and fifth ribs *soft friction*, distributed for a few centimetres, also upon the *left side* at about the same area. *Indistinct extrapericardial friction*. Respiration painless, quite free. The edema diminishes. Low temperature, no delirium. Lassitude, decided signs of malaise. In the afternoon the temperature of the body rises to its former height.

February 8th: During the night an eruption has developed. Color, pale to bluish-red, closely resembling erysipelas, in that the borders show serrated processes and are sharply defined.

Differences: Decided swelling of the subcutaneous tissue, intermingled with edematous areas are quite pale islets, then small areas extending even beyond the median line. *Seat*: February 6th, the eruption, resembling streaks, like welts caused by the blow of a whip, extend over the edematous parts and even beyond these in the region over the left shoulder joint, and upon the right to the upper half of the scapula. During the course of the day there is a formation of smaller and larger vesicles up to the size of a hazel-nut—the *exanthem* increases up to February 14th, at which time death occurs, being preceded by a slightly painful edema which is followed after longer intervals, lasting up to thirty-six hours, by erythema and inflammation, with vesicle formation.—The autopsy gave the result mentioned above.

A disease which *distributes itself in the peculiar manner*: First, a development from the throat to the mediastinum and the pleura, as well as to the

¹ Ueber Mandeln und Balgdrüsen. Virchow's Archiv, Bd. xcvi, p. 211 ff. (1884).

subcutaneous tissue of the cheek and the upper half of the body, then increasing in a very irregular distribution but constantly in connection with the existing morbid foci, *showing the road taken by the pyogenic cocci*. Frequently this is not so distinct and it may become questionable *whether an inflammation of the structures of the pharynx from other causes may have opened the tract for the microbes of sepsis*. The decision here, as in other cases, is especially difficult in that *the pyogenic cocci need not bring about a disturbance alone at the point at which they have entered*. A rupture of continuity of the tissue may heal without reaction, and an incised wound may close completely, nevertheless, it has made infection possible. There are proofs enough of this, such as the following:

OBSERVATION II 1

Sepsis after injury at the autopsy of a woman having died of purulent peritonitis. Purulent edema of the left half of the body, bilateral purulent pleurisy, as well as mediastinitis and pericarditis. Death. Streptococcus infection.

A student of medicine injured himself on October 26, 1885, on the ring finger of his left hand upon the side next to the middle finger. It could not be accurately ascertained whether this was caused by a cut or whether he injured himself upon the roughened margin of the ribs at the autopsy of a woman who had succumbed to purulent peritonitis.

Upon the day following, lassitude and general malaise. In the course of the twenty-eighth day of the month, upon the posterior surface of the left hand six pustules appeared that ruptured on the next day, yellow pus flowing from them. On account of severe pains in the left axilla and marked fever, the patient was taken to the Tübingen hospital upon October 30th.

There was found: Upon the ring finger of the left hand, adjoining the middle finger, a lentil-sized tear or cut surrounded by a small red margin. Upon the back of the hand some red macules about the size of a lentil seed, but all of them beginning to pale.

In the arm *no sign of lymphangitis*, but *the skin of the axilla is reddened*, showing a *somewhat diffuse infiltration of the lymph glands and their surrounding tissues*. These areas are painful upon slight pressure. In the course of the *next days: yellowish discolored areas the size of a dollar upon the left side from the axilla to the ilium*, which, on becoming confluent, formed edema which distributed itself over the entire left half of the back. *Jaundice, nephritis*, varying rises in temperature up to 105.8° F., finally the symptoms of great weakness and stupor, death.

At the *autopsy* (Prof. Nauwerck):

"Beside the nail upon the ring finger of the left hand, a very slight cut wound. Nothing noticeable upon the arm, only beyond in the axilla are the cutaneous coverings and the subcutaneous tissues diffusely swollen. The pectoralis major and the other muscles in the immediate vicinity are densely permeated by a serous fluid so that the muscles are traversed by yellowish white striæ. The nearer the axilla is approached, the denser the infiltration, here and there taking on a strictly purulent character. The axillary lymph glands are somewhat enlarged, show a moist cut surface, which is partly pale but here and there reddened. The tissue, surrounding these glands, is found to be of a yellowish-white color and purulent."

In general, a wide distribution of purulent phlegmons. Details are here of no special interest.

In another instance of my own observation (III), in the case of a woman whose thumb had been bitten by a calf, the mark being almost imperceptible, *only after eleven days there developed without lymphangitis, a rapid infiltration of the axillary glands, with severe general phenomena*. The small

¹ From Dennig, Ueber septische Erkrankungen, Leipzig, F. C. W. Vogel, 1891.

wound at that time had healed completely. It was a case of *streptococcus infection* with multiple foci in the pleura, the lungs and the kidneys, which *forty-eight days after the injury* terminated fatally.

The case is to be explained as follows:

Feebly virulent cocci, which, if they be introduced in small quantities, only form foci by proliferation after a prolonged lodgment at a point removed some distance from their port of entrance. These are now, in fact, the starting points of the active infection which may have originated anywhere else in the circulation of the lymph-tracts and may not even always implicate the lymph glands that are in immediate connection with this chain. Such slight abrasions upon the surface of the mucous membrane do not leave visible cicatrices.

The results of the investigations of Ponfick are very surprising. He found at the autopsy, *in 100 children aged from one month to four years*, who succumbed to various diseases, *78 times bilateral, and 13 times unilateral, otitis media*; only in 9 cases was the middle ear normal. Schuchardt,¹ from whom I take this report, is entirely right in including them with an !—It is quite probable that pus cocci extremely frequently find their entrance from the oral and pharyngeal cavities, form foci in the tympanic cavity but perish here without producing more than locally circumscribed and, in the majority of cases, not especially severe disturbances. For how rare in comparison to the entrance is the development of a general infection. It is possible that infection occurs, that the cocci find their way from the middle ear into the circulation without having shown their presence there, and we should then speak of a *sepsis from unknown causes, a cryptogenetic sepsis* (v. Leube). In those cases terminating in death this possibility should be thought of and at the autopsy it should be carefully searched for.

The realm of cryptogenetic sepsis is becoming more and more limited. Of fundamental importance in relation to this is the answer to the question:

May pus cocci from a previous infection remain anywhere in the body for a long time without producing symptoms, then from the old focus again cause renewed, perhaps severe symptoms, general as well as local?

First, the facts which result from simple observation. It is best to take *osteomyelitis* as an example, for in this disease the disturbances in their appearance may be recognized to some extent. That they are due to pus cocci, especially to the *staphylococcus pyogenes aureus*, is certain. Now experience teaches the following:

It happens, even though rarely, *that a long time after recovery from osteomyelitis has occurred, with slighter or more marked disturbance of tissue, that renewed disease appears, as a rule, in the bone that was affected in the first attack.* Garré² reports 3 cases from the surgical clinic in Tübingen, in one of which the relapse occurred twenty-nine years afterward—here the spontaneous cure had existed for eighteen years—twenty-three years and six-

¹ Die Krankheiten der Knochen und Gelenke, 1899. Deutsche Chirurgie, Lieferung 28, p. 165. Hier auch die ganze Literatur über Osteomyelitis.

² Ueber besondere Formen und Folgezustände der acuten Osteomyelitis. Beiträge zur klinischen Chirurgie. Herausgegeben von Bruns, Czerny, u. s. w., 1893, Bd. x, p. 241 ff.

teen years in the two other cases, later. Still more remarkable is the following observation of Dr. Kurt Müller¹ in Erfurt.

OBSERVATION IV

The patient, aged sixty-three, fifty years previously suffered from osteomyelitis in the lower diaphysis of the femur upon the right side. For a long time thick pus had flowed, ankylosis having been permanent in the knee-joint. *No other affection had occurred during the entire intervening period.*

Since the last few years "*rheumatism*," interrupted only by brief periods of rest, often with great pain in the right leg. Dr. Müller diagnosticated *relapsing osteomyelitis*. At the operation there was seen in the *greatly thickened, very compact thigh bone, a large cavity that was filled with greenish-yellow pus*, besides numerous small abscesses were found in the tibia. Culture showed the presence of the *staphylococcus pyogenes aureus* which was successfully inoculated into rabbits.

Dr. Müller himself served as an unwilling test, for after operating, a great number of small furuncles formed upon his hands which had been in contact with the pus for some time. A similar case is reported from the clinic of Albert in Vienna.²

In close connection with these cases are those in which the *scars in injuries to bones*, especially gun-shot wounds, are after a long period of time the points of origin for general sepsis. Here it appears to be of importance that foreign bodies—particles of cloth, parts of the bullet, etc.—being embedded are retained. This happened in the observation of a case in my private practice:

OBSERVATION V

Gun-shot fracture of the right thigh. Complete undisturbed health for eighteen years. Rapidly appearing sepsis, taking its point of origin from the old scar, with a fatal termination after fourteen days. Ichorous abscesses in the right upper and lower leg. Particles of lead enclosed in the old scar. (Pathologist, Prof. Nauwerck.)

The patient, a strong man, received a severe gun-shot wound in the right thigh at the battle of Vionville—August 16, 1870—which healed, leaving a shortening of a hand-breadth in the leg with deep retracted scars. In these there has always been some sensitiveness to touch. Outside of this, the injured leg was capable of complete use, not only for prolonged standing and walking but even for riding and dancing.

Upon Dec. 14, 1888, sudden malaise, chilliness and soon a decided chill. *Upon the next days* the pains in the right thigh became more severe, besides those in the scars, typical sciatica also developing upon the right side. An effusion occurred into the right knee-joint, followed by a uniform swelling of the entire leg. Death occurred upon December 27th, with the signs of cardiac asthenia.

A careful search was made to ascertain whether a fresh injury, no matter how insignificant, might have been present. None such was found.

Among *the diseases of the internal organs*, those of *the heart*, especially of its *valvular structure*, must be primarily mentioned. Of the greatest significance for us, are those cases in which, *after a period of complete latency, rapid general infection occurs from a quiescent focus*. These cases are no more frequent than the two other observations just reported.

¹ Ueber Knochenabscesse. Archiv für klinische Chirurgie, 1897, Bd. lv, p. 782 ff.

² Regarding the finding of virulent staphylococci in an osteomyelitic focus which had been closed for thirty-five years, see Dr. Julius Schnitzler. Centralbl. f. Bakteriologie und Parasitenkunde, 1894, Bd. xv, p. 270 ff.

OBSERVATION VI

Slight insufficiency and stenosis of the mitral valve, slight degree of hypertrophy of the right ventricle. The time of the development of the affection could not be determined. Compensation apparently not influenced. Sudden attack with general sepsis, fulminant course, lethal termination in seventy-five hours. Recent endocarditis, small foci in the lungs, in the kidneys, in the stomach. Streptococcus infection.

Man aged fifty-eight, who reports that he had never before been sick, was suddenly attacked by a severe chill, at midnight between the 27th and 28th of February, 1890. In the morning he attempted to get out of bed but was unsuccessful. As it was believed that he was suffering from influenza no physician was called until the morning of March 2d, when the patient was admitted to the hospital. Upon admission: high grade of asthenia, insensibility, involuntary evacuation of urine and feces, temperature 106.3° F., irregular pulse (110), increased respiration (39). No marked signs in the cardiac area, slight dulness in the upper part of the right lower lobe of the lung. Death occurs in coma, upon the morning at three o'clock upon March 3d. *The necropsy* (Prof. v. Baumgarten) revealed: Well developed heart. The musculature of the right ventricle shows a slight degree of hypertrophy, the mitral area shows a mild grade of insufficiency and stenosis due to connective tissue shrinkage of the valves in their longitudinal and transverse diameters, as well as a coalescence of both leaflets by a calcareous scar-tissue bridge.

Upon the free border of the aortic leaflet of the mitral valve some small grayish, fibrin-like excrescences about the size of a pin-head. The tendineæ of the aortic leaflet greatly thickened, at the border between the posterior and left aortic leaflet a smeary, gray, slightly adherent deposit of small extent is noted.

Thus, an old focus, which, as the resulting phenomena showed, produced but slight functional disturbance—only slight hypertrophy of the right, none of the left, ventricle—permitted the development of streptococci anew. These microorganisms were found in great profusion over the rest of the body—lungs, kidneys and stomach—and by a general infection, brought about a rapidly fatal termination.

We have learned to recognize in this and similar cases the fact that *the seat of previous disease may be the starting point for a later affection*. The obvious conclusion appeared justified: *Germs remained*, which for a long time were inactive, having, however, retained their property of life, and under favorable circumstances of renewed activity.

But this opinion is not generally accepted as correct. The following view is contrasted with it: *Recent infections are brought about by the fresh entrance of pyogenic cocci and their accumulations which have entered the blood from any source in the tissues previously affected*. These tissues offer a predisposed basis which has been changed in a special manner. Garré who agrees with the opinion of Kraske, who deduces this from diseases of the bone, amplifies this somewhat more minutely:¹

“For the postulate of a new hematogenous infection, the localization at the old area appears at first sight to be strange. If we reflect what a conspicuous change in the capillary area of a bone is brought about by a severe purulent inflammation, that in the cicatrix permanent capillaries of narrower caliber or with irregular dilatations (capillary aneurysm) are present, it will

¹ *Loc. cit.*, p. 271.

be understood that such mechanical hindrances and local circulation anomalies decidedly favor the deposition of microorganisms from the blood."

For the circulatory conditions of the blood in the valves of the heart that have been altered by endocarditis which favor the influx and accumulation of microbes in these areas, Köster¹ had already previously given this opinion and defended it.

I should not like to give an opinion as to what is correct. Certainly an observation such as Schnitzler's gives a very convincing impression: In a sacculated sclerosed bone, of at least 2.5 cm. thickness, virulent cocci were found in the cavity. How could these have reached this region from the blood?

But: In this patient there existed from the previous and now again affected, area, since August, 1892—the operation in which the cocci were found occurred on December 12, 1893—from time to time severe pains and a febrile movement. *Therefore, signs of a local as well as general, relapse for longer than a year.* The defender of the opinion, that germs remained, must explain how they found their exit from the closed cavity, and at that during a period lasting longer than a year. The defender of the view of a new infection must show how the *microbes found entrance*.—Then this view must explain whence a new emigration took place and the other view why a renewed activity of the microorganisms occurred?

The questions are not as yet clearly explained. First, in my opinion, it should be shown how the conditions can actually exist in such cavities which are "sacculated and enclosed." This closure cannot be complete; otherwise, whence does the pus come that is contained in it? The pus shows a connection with the blood from which it originates.

We are completely at a loss to explain why septic infections vary so greatly in intensity at different periods.

A long time prior to the present period of anti- and aseptic methods of operation, in the surgical as well as gynecological clinics, it was known that the number of patients affected by pus fever declined almost to a complete disappearance without an assignable cause and at other times markedly increased. This even gave cause to postpone every operation which was not absolutely necessary to save life to a more favorable period.

In the case of sepsis with an unknown port of entrance, in spite of my comparatively great amount of clinical material, I have observed the same conditions. Since the beginning of the year 1880 the affections are increasing which I only saw sporadically in the form of malignant endocarditis. First these cases mostly terminated fatally, then other local affections followed with another clinical picture, recovery also occurred. In the course of time the symptoms became milder, there being only now and then a fatal case. Thus, I found an opportunity to observe this extraordinarily changeable disease, in so far as it is possible for a single individual. New forms were constantly appearing which were previously unknown to me. *Vita brevis, ars longa*, if anywhere this will be recognized here.

It may appear strange that I extend the realm of septic infection to such a great extent. Autopsies, which are never omitted, observations, which

¹ Die embolische Endokarditis. Virchow's Archiv, 1878, Bd. lxxii, p. 274-275.

extend over many years, permit this, for, I have more frequently failed to recognize sepsis than to suspect it where it was actually absent.

The *period of incubation* from infected wounds is but a few days. Whether this is correct for all kinds of contagion is unknown.

PATHOLOGY

Regarding the *morbid anatomy*, there is, in general, little to relate.

Primarily, the conditions and damage to the tissues that occur in general in the acute infectious diseases are found more or less developed according to the course of the disease. With these, the inflammations and necroses due to the particular morbid agent are noted which are in keeping with its distribution everywhere in the body.

The grade of these changes varies greatly: Inflammation in its first stages up to suppuration and hemorrhages, perhaps in one and the same case. Destruction of the severely affected tissue, complete cure in those affected to a slighter extent. *Every focus is a substantive unit independent of others.*

It is quite possible that tissue necroses which do not go hand in hand with inflammatory changes are due to *toxins* produced by metabolism of the pyogenic cocci.

If the *disease has existed for a longer time* then, in the implicated areas, those alterations have appeared which we are accustomed to observe after inflammations and degenerations. Now actual organic lesions may be present which independently of their etiology may in themselves make their influence felt. I need only call attention to the valvular lesions with their local as well as constitutional sequelæ, the results of endocarditis.

SYMPTOMATOLOGY

We must now devote our attention to the general clinical picture.

Only outlines can be given; in some cases the condition is well developed, in others but slightly indicated, but, even here, it is recognizable to the trained eye. And, at the onset, the recognition of the true nature of the affection is of the greatest value, for there are not many diseases in which, before any one organ is positively recognized as the seat of the disease, the nature shows itself in so many different ways.

General malaise, frequently with a sensation of marked illness, often combined with lancinating and dragging pains in the limbs, lasts for several days. With this, mild febrile movements are combined. Chilliness and chills, irregularly appearing during all times in the twenty-four hours, show themselves. The patients believe that they have taken cold, and are strengthened in this opinion by an angina not infrequently present. Periodic improvement alternates with an increase of the symptoms. Thus, the onset of the affection may develop slowly without distinct signs, but more frequently the disease is ushered in by a more or less severe chill, which is soon followed by decided fever. Now the patient certainly takes to bed and the physician is called even if this has not occurred previously.

Upon examination there is found: pallor of the face, with a slight bluish

discoloration, especially marked about the lips and around the mouth. The respiration is frequently only in proportion to the height of the fever, the pulse, however, often markedly increased. The impulse of the heart is diffused, striking with force against the thoracic wall; in proportion to its labor, the filling of the pulse is in decided disproportion.

Nothing abnormal upon percussion, but there is soft friction upon auscultation of the lungs in different areas, at one point more distinct upon inspiration, at others more noticeable upon expiration, and at the third place uniformly divided between inspiration and expiration. If some pressure is made with the stethoscope, the sound becomes louder, but the sign is not accompanied by pain, at least not by severe pain. The friction is irregularly distributed, the individual foci are separated from each other. Over the *liver* and the *spleen* the same friction is often audible, more rarely, on the other hand, upon cardiac movements.

The *cardiac sounds* are loud but dull, accompanied by functional murmurs of all grades of intensity.

During this period *catarrh* of the medium or finer bronchi may be present, but it is irregularly distributed. The *spleen* is somewhat enlarged.

The *bones are sensitive to pressure*, especially the long tubular bones, in the majority of cases. It is necessary to push aside the muscles and to press the bone with the tip of the finger to determine this with certainty; at other times, any, even the slightest touch, is painful, therefore each movement is accompanied by pain. Usually in one and the same bone foci, which are separated from one another, are noted, exceptionally the bone is affected in its entire extent.

If the *articular ends* are affected—this is not necessarily the case—then the joint in question shows some swelling as do also the surrounding soft parts. In this area severe phlegmons may develop, being local, but also, more rarely, distributing themselves so that great danger to life is produced. The *flat bones*, those of the skull or of the pelvis are only rarely implicated. The half joints, especially those between ribs and sternum, are more frequently affected.

At other times all these inflammatory signs are irregularly distributed over both halves of the body. Constipation is much more frequent than diarrhea.

Constitutional disturbances are never absent, perhaps a loss in weight may be noticeable early, but certainly the capacity for work is decidedly diminished; the feeling of lassitude increases.

The *height and distribution of the rise of temperature* during the day is subject to great variations; *in rare cases fever is absent*. *Anorexia* is always present.

The *general impression* that is conveyed by the patient is that he is suffering from a *severe constitutional disease*.

And what occurs now?

This depends for the most part on how far the organism, as a whole, is affected, and further, the clinical picture in the individual case depends upon the organ in which the pus cocci have collected and the extent of their dissemination. Neither is at any time sharply defined, and it is self-evident that variations, even a complete change in the symptoms, occur again and again.

It is well to divide the affection into **groups** so that a general insight may be gained. I have chosen the following division:

I. *Group in which the general phenomena are most prominent.* Rapid decay and death as in any other severe infection. An example of this kind has already been given (see Observation VI.).

II. *Group in which the cardiac implication is most prominent.* Rarely is the inflammation limited to the myocardium, endocardium or pericardium; it is best to speak of **pancarditis**, and in the individual case an attempt should be made to recognize the most markedly implicated part.

III. *Group of predominant implication of the bones and joints.* In this category belong the severe forms which have been known for a long time: *Bone or joint-typhus* as they were called by Chassaignac, now usually designated, according to Lücke, as *primary, infectious, osseous and periosteal inflammations*. The *metastatic arthritic inflammation* in the old clinical picture of pyemia belongs to this group.

In the milder forms we must differentiate between the “rheumatic” affections and, above all, from acute articular rheumatism.

IV. *Group in which inflammations of the skin and the subcutaneous connective tissue and in the muscles is predominant*, thence affecting the *mucous membranes and the serous membranes*. The severe forms—*acute septic phlegmon* is the name of a pyogenic cocci infection which has been recognized for some time—gradually change into the milder variety. Any one wishing to do so may make subordinate divisions, but I, myself, believe that the general division is sufficient.

V. *Group in which inflammation of the internal organs is predominant: brain, lung, kidneys, spleen, liver, stomach and intestines.* Here the disturbance in the activity of the affected organ is most marked in the morbid picture, often to the extent that it completely dominates the situation.

I do not believe a further division into groups to be necessary, scarcely desirable. An affection of the nerves might be considered, but I have rarely found them to be at all isolatedly affected, and still more rarely have I found the symptoms on the part of the nerves to be the main ones; they are usually designated by the term “functional.” However, I am quite willing to admit that in this instance other opinions may exist.

I shall be brief in the discussion of individual symptoms, as I intend to devote *considerable space to the differential diagnosis*, for this is of the greatest importance in practice. Of especial importance is the observation of the *temperature of the body*, for this reason I shall go into details.

In septic infection the temperature curve, according to the results of observations (I refer constantly to rectal temperatures), is *so irregular* that to exhaust all possibilities we must say: There is no type which can be excluded.

The *absolute variations* of temperature which have been ascertained, vary between 109.4° F. and 93.5° F. A definite comprehension can be gained in the following manner:

The *temperature of the normal individual* averages for the twenty-four hours about 98.9° F.; as a rule, the temperature rises from morning to evening and falls from evening to morning: A higher range than 100.4° F. is not

found in health as long as no strenuous muscular activity is exerted. The medium temperature for the day is strictly adhered to, if transitorily—by muscular labor, for example—higher ranges are reached, lower ones follow (law of compensation). Thus, the distribution of the temperatures during the hours of the day may be transitorily altered.¹

These conditions are changed if a living pathogenic agent displays its activity.

Now the rule is broken, higher averages are shown: Sometimes, but not always, it occurs that the highest figures are immediately followed by the lowest ranges. This is independent of the time of the day. In general, it may be said that the activity of the pathogenic agent is shown by the temperature.

In the case of the malarial plasmodium this is unquestioned. And what is true of these is true of pus cocci. Their invasion makes itself noticeable in varying high degrees, occasionally to such an extent that the temperature curve closely resembles that of a malarial intermittent (Figs. 45 and 46). It may also be that continued high fever occurs, as in the severe forms of malaria. Then again, as may take place in a gradually developing malaria, only transitory slight rises being noted. The life duration of the pus cocci inside the body is not limited to a special time, neither is their power of multiplication, the increase or decrease of their power of life (virulence), this is not regulated according to any known law.

If with this the very varying resistance of the septic patient is diminished greatly, it is then obvious why the temperature curve is liable to such extraordinary variations in sepsis.

Not only for diagnosis, but also for treatment, is it of great importance

¹ See Jürgensen, Die Körperwärme des gesunden Menschen. Leipzig, F. C. W. Vogel, 1873. The investigations of my pupils. H. Jäger, D. Archiv f. klin. Med., Bd. xxix. P. Steffens, idem., Bd. lxii.

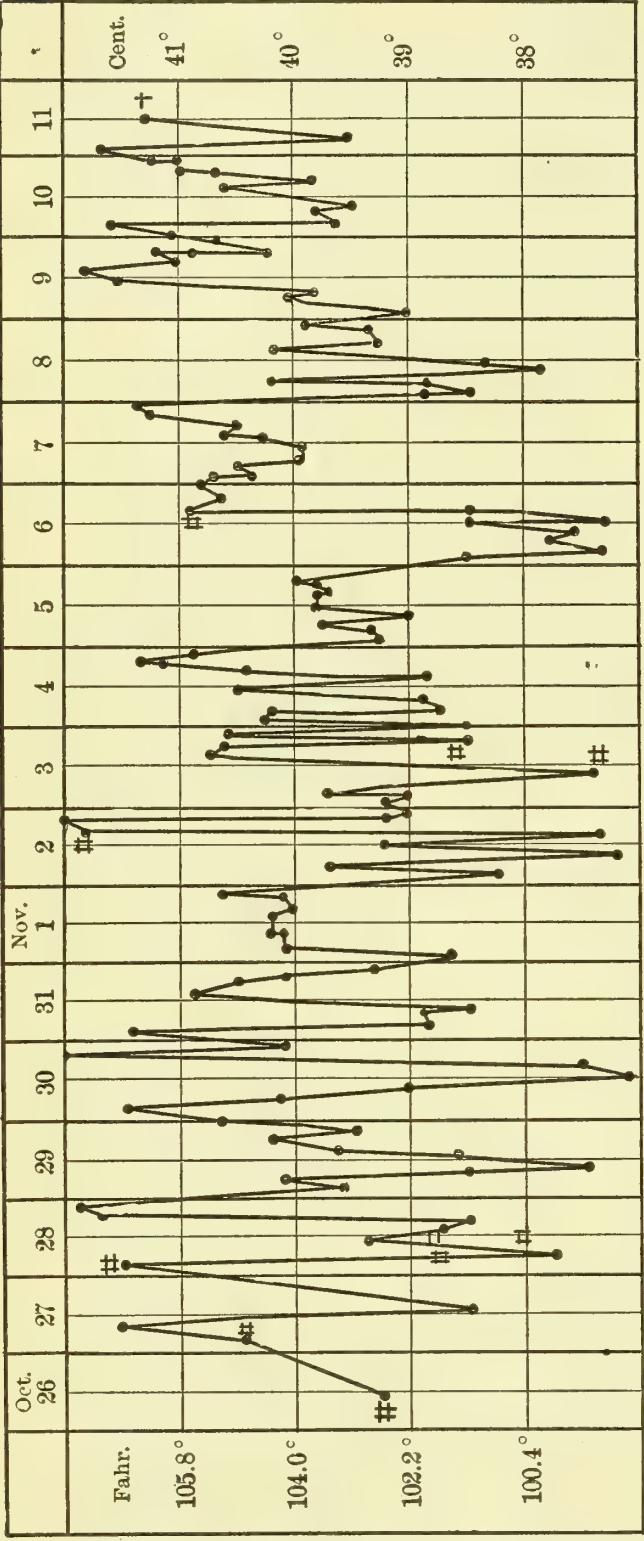


Fig. 45.

#Chill

to know that the presence of active pus cocci in the organism may alone show itself in the fact that the distribution of the temperature during the day may deviate from the normal (Fig. 47). Without being absolutely increased, its height upon the succeeding days may at one time occur in the morning, at another time at noon, and again in the evening, the lowest point varying in a similar manner.

The *milder infections*, with localization which can only be recognized with difficulty, as often enough occurs in the heart, *betray themselves by these conditions*. *New outbreaks* are to be expected, although everything appears to be in order when this condition of the temperature becomes noticeable.

The *cardiac activity* is most commonly disturbed; whether this is due to demonstrable damage can not always be decided at once, perhaps only after a longer or shorter period of time.

Most frequently *cardiac unrest* is present early: The apex beat is diffused, striking powerfully against the thoracic wall. The period between the individual contractions appears to be shortened, not corresponding to their actually increased number, an uninterrupted heaving and falling is seen and felt. The *muscular sounds* may become so strong that they may be heard at some distance; more often dull, not especially loud and demarcated sounds, resembling murmurs, or accompanied by such, are heard.

The *labor performed by the heart does not appear to be in proper proportion to its effects*: The pulse is not well filled, decided cyanosis becomes noticeable; the nose, ears, fingers and toes become cool. Irregularities in the dilatation and sequence of the pulse-beat are also not infrequent. Decided deviations, usually designated as functional or nervous, may appear—thus bradycardia may take place. We should always be careful in our opinions as to whether gross disturbances of tissue are present or not. Nor is it well to be too pessimistic; a certain weakness and an increased irritability of the heart may remain for some time without any serious consequences developing.

Well developed diseases of *the bones and periosteum* belong to the domain

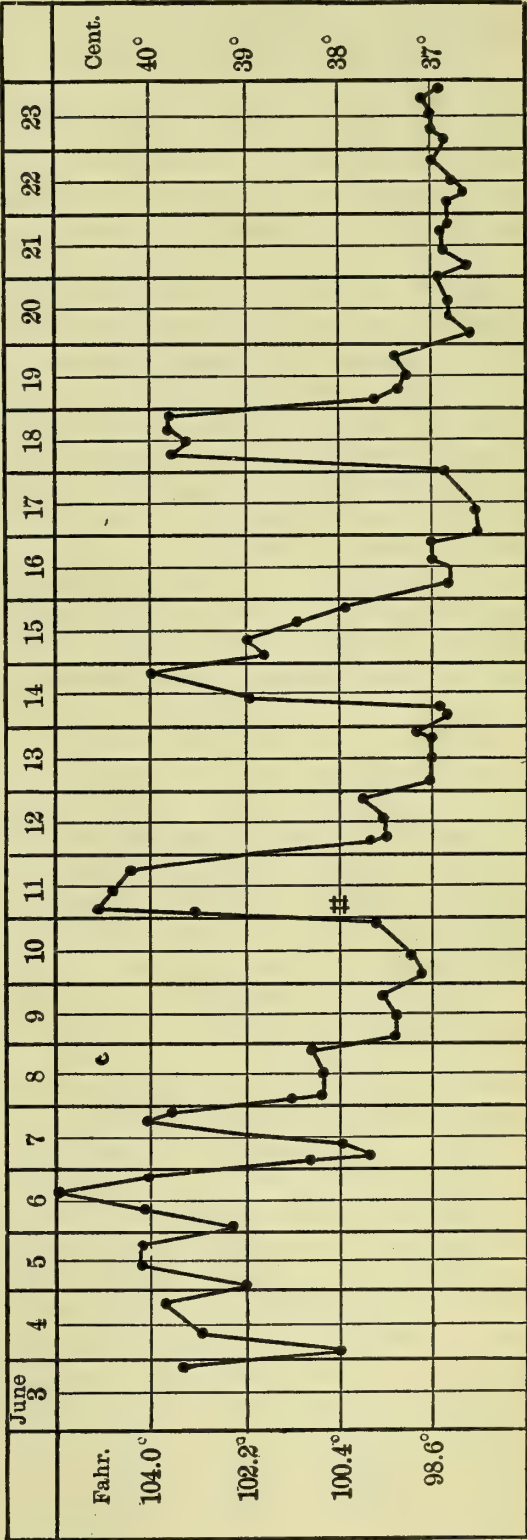


Fig. 46.

Chill

of surgery, which, fortunately, has attained brilliant results in the case of sepsis. The milder forms, in which but a slight local affection occurs, have great diagnostic importance. Naturally, the mild forms may change into the severe ones suddenly, and bone typhus, with all its horrors, result.

Disease of the *joints*, which do not appear as severe metastatic suppurations, are usually in immediate connection, as it appears, with their epiphyses. It is difficult to differentiate the condition seen in the typical form of rheumatoid arthritis. It is certain that a very mild grade of inflammation occurs which still permits the use of the joints.

Inflammation of muscles, as individual foci which terminate in pus formation, are not very frequent. That they occur in sepsis can be doubted as little as that well distributed suppurations of muscles are connected with phlegmons which invade the tissues deeply. On the other hand, it is not easy to correctly designate what we mean by muscular rheumatism. v. Leube¹ is of the opinion that the condition is due to infection by a toxin which is closely related to that of acute articular rheumatism. Its relations to pyogenic cocci are now frequently mentioned (see page 669). Thus, etiologically, a connecting link would have been formed. At all events, it is certain in the

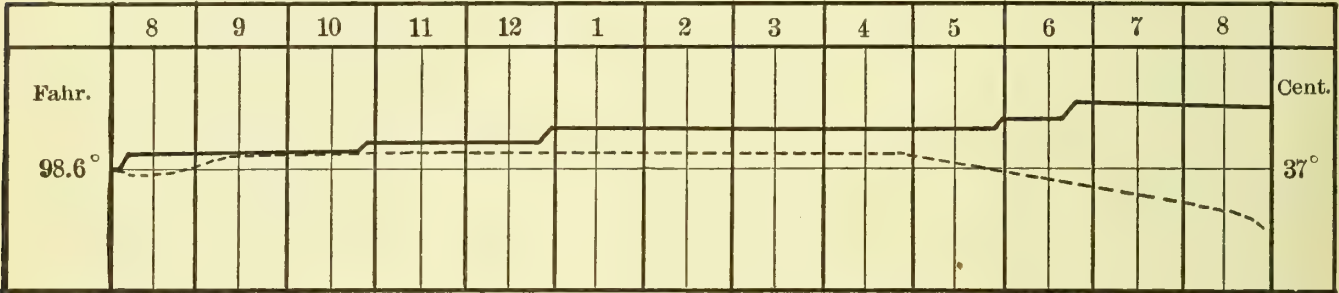


FIG. 47.

onset, as well as later, that *diseases of the muscles may occur in well developed cases of sepsis*, which, clinically, cannot be differentiated from rheumatism. Personally, I share von Leube's conception; to what extent this is correct the future will tell.

Erysipelas, streptococcus infection of the skin, as a rule, not distributing itself further than this, and, besides, the inflammation only producing constitutional disturbance, is described as an especial affection. And for this there are many reasons. More rarely does "*malignant*" erysipelas show itself in the severe septic diseases.

As an accompanying condition of sepsis, we see a *great variety of eruptions* which vary greatly regarding their form and appearance. In general they have the character of inflammation as does everything that is due to pus cocci, and just so do they show the most varying grades of the inflammatory process; simple *roseola*, *urticaria*, perhaps but a slight eruption, which rapidly appears and disappears. The more developed forms resembling *erythema exsudativum multiforme* and *erythema nodosum*, may occur isolatedly but also reveal great distribution, showing themselves in varying grades of development.

Von Leube saw a condition resembling *scarlatina*—which probably was formerly looked upon as true scarlatina (compare page 676)—he also reports

¹ Beiträge zur Pathologie des Muskelrheumatismus. Deutsche med. Wochenschr., 1894, No. 1.

having seen pustules which resembled those of smallpox. I have not seen these, but have very frequently noted pustules upon the skin, larger or smaller, few or many.

Hemorrhages into the skin also occur—they are not only punctiform, sharply demarcated, but also show wide distributions with irregular borders, and, if they occur in repeated relapses, may be of all colors which hemoglobin shows when not exposed to the air.

Upon the *mucous membrane of the mouth and the pharynx*, eruptions resembling those upon the skin, as well as hemorrhages are noted, but by far less frequently.

The importance of the *tonsils* as the point of entrance has already been mentioned. We see angina as the first symptom comparatively often and in almost every form. Is it produced by the pus cocci that have already entered, or does it only open the door to them? Both are probable. Attention has already been directed to the seriousness of the inflammation of the structures of the pharynx as the point of entrance for a condition which may develop into phlegmons, this being widely distributed. (Observation I.)

Disease of the *serous membranes*, which, as has already been mentioned, is so usual at the onset and is so widely distributed, thus of the pleura, the coverings of the peritoneal cavity and those enclosing the organs contained in it, in which small foci are produced, have great diagnostic importance on this account. Very rarely are deep-seated *severe inflammations* noted in these regions. *The pleura* is the serous membrane most often implicated, but even when effusion takes place it is usually not large, being, as a rule, serous and absorbed in a comparatively short time.

Massive purulent exudates, which are by no means rare after traumatic sepsis, are, according to my experience, only exceptional in the cryptogenetic forms. Empyema is more frequently found as an accompaniment of serious disease of the lungs, of the pericardium, of the mediastinum, of a phlegmonous condition of the thorax. It may also occur from an implication of the peritoneum, the disease having found its way through the diaphragm. Under all these circumstances, the effusion may be *hemorrhagic*, possibly *ichorous* also.

Collections of pus in the abdominal cavity—quite common in puerperal infection—I have only seen in connection with foci due to embolism.

The *meninges* of the brain and spinal cord, in the form of well-developed, diffuse, purulent inflammation, has only been noted exceptionally in my cases. Do similar circumscribed areas to those in other serous membranes develop here? According to my observation I could almost assume this.

The spleen, as a whole, is immediately affected by the infection. To this must be added that an endocarditis may give rise to embolism in the spleen, with all of its consequences.

Regarding the *liver*, very little can be reported, in my experience it was but slightly affected. Jaundice which has such great importance in traumatic sepsis was but rarely noted.

The *kidneys* are invariably implicated to some extent, in so far as albumin is excreted in quite large amounts. Besides this, *inflammation of all forms* is noted in the kidney itself and in its pelvis. I must not enter into this

interesting condition more minutely, but it is *quite remarkable*: uremic phenomena may occur even in a circumscribed inflammation, damaging but a part of the tissue of a kidney severely and permanently. Diffuse acute nephritis due to sepsis, may result in complete cure, but contracted kidney may also develop from the condition.

Focal disease due to coarse emboli take an especial course according to whether or not the emboli contain virulent properties.

The *digestive organs* are always functionally, often enough but transitorily and slightly implicated, organic affection is rare. Anorexia, which may become very marked so that the patient must be very carefully fed, as severe vomiting which is difficult to stop may appear. Constipation is comparatively more common than the opposite condition, which is certainly not remarkable. I have never observed *massive diarrheas of puerperal sepsis*. Marked changes in the mucous membrane of the gastro-intestinal tract, as proved by autopsy, do not occur, *as a rule*. Hemorrhagic inflammation, occasionally hemorrhagic infarct, have been observed. I have seen *intestinal hemorrhages* and not insignificant ones at that. What destruction of tissue caused them, I am unable to say, as the cases recovered.

It now remains to report regarding *the lungs*. *Bronchitis* is frequently present from the onset, the medium-sized and finer tubes are affected; this usually occurs more in separated foci than in an uninterrupted connection, always preferably affecting the lower lobes.

In cases of severe capillary bronchitis, *pulmonary collapse* and true *bronchopneumonia* occur; if the condition has lasted for some time and the heart has become weak, *hypostasis* takes place.

These, as well as *infarct* and *abscesses of the lungs*, which are the result of emboli, show the course which is peculiar to them, they present nothing special.

Worthy of mention are the *inflammations* produced by the *entrance of microbes through the blood into the lungs*. They occur rapidly, develop like an ordinary pneumonia, but do not go beyond the stage of engorgement. Here a focus may remain, here another one disappear, the entire process with its symptoms resembling *wandering pneumonia*. I have frequently enough at the onset made this incorrect diagnosis. An entire lobe of the lung being the starting point of the process may become solid and show all the physical signs of consolidation. Whether these are mixed forms—accumulation of Fränkel's pneumococci—I do not know. That streptococci are sufficient to cause them, the previously mentioned case proves (Observation VI).

All, even foci of great extent, in the majority of cases, show recovery, the lung attaining its previous normal condition. In some areas the tissue must have suffered, for we have seen pneumothorax develop. This patient recovered, but in another fatally terminating case, pneumonic abscesses were present, of which several had ruptured. This may have been the case in the previous patient.

A *functional disturbance* in sepsis is quite usual. The *respiratory frequency is increased* often to such an extent that the proportion between the pulse beat and the number of respirations, which normally should be $\frac{P}{R} = 4.5$ (normal, 81 to 18), becomes smaller and may fall to $\frac{1}{1}$.

At the onset this is usually absent but in a comparatively brief period the condition appears. Disease of the respiratory passages or of the respiratory organs need not be present, at least there are no causes that would serve to explain this condition. The disturbance is not due to the severity of the affection or to any distinct localization, on some days it may be stronger or more developed than on other days, at times it may be absent altogether, afterward reappearing again. I mean that we cannot avoid reflecting upon an *immediate action of the septic poison*, the products of the metabolism of the pus cocci, upon the *respiratory centres*. In the diagnosis of mild cases, which for a long time run their course without localization, especially of endocarditis, this sign is not without importance.

With this the possibility that the increase of the respiratory frequency in sepsis—a fact that has already been noticed by von Leube—is in connection with the toxic action upon the central organs, must be admitted, as this frequently occurs:

First, it must be remarked that neither the absolute height of the temperature nor a marked fall of the same go hand in hand with true cerebral phenomena, as is the case in many other infections. Headache becomes severe early, coma is soon added, and occasionally also illusions and hallucinations which may find expression in the wildest attacks of mania. In a certain sense, the change from excitement to exhaustion, which occurs without an assignable cause, is very conspicuous.

Naturally, nothing definite for purposes of diagnosis can be taken from this. Often the well-developed picture of purulent meningitis is present—but nothing is found in the brain—at other times exactly the same symptoms and the severest encephal meningitis is present. It is well known that this may occur in any infection, and we are justified, in a negative anatomical finding, in speaking of “*intoxication*.” The *emboli* carried into the brain in endocarditis, according to the degree of their virulence, cause various focal phenomena, to which we do not intend to refer in detail.

A purulent inflammation of the *cerebral meninges* is usually associated with a similar condition in the membranes of the cord, at least in its upper portions. This rule shows no exceptions in the case of sepsis.

Special disease of the spinal cord in the form of distinct, well-developed tissue disturbance may occur, but it is rare—I have only once seen a *transverse myelitis* in connection with endocarditis.

With *disturbance of the function of the spinal cord* and some *neuroses without known cause*, which are distributed over the nervous system, the conditions are different. I shall include both and enter somewhat more into detail because the condition is less known. It may have been accidental that in the last years in which sepsis appeared to show a milder course in comparison with former times, I have seen these disturbances more frequently.¹

It has been noted for a long time that *chorea* is in close connection with endocarditis, as well as with sepsis and classical acute articular rheumatism. Besides chorea and endocarditis, and when the signs of sepsis were present, I found *cataleptic conditions*.

¹ See Jürgensen, Endokarditis. Nothnagel's Handbuch, Bd. xv, i, iii.

Further, there were *rapid changes of the reflexes*, which in the same patient were at one time stronger, at other times weaker. This occurred in the case of the reflexes of the skin, as well as in those of the tendons; they did not, however, run parallel, but, throughout, were independent of each other. The proportional frequency in which the "*paradoxical phenomenon*" of Westphal appeared was conspicuous. It can be demonstrated in the following manner: Rapid and strong dorsal flexion of the foot of a patient while lying in bed allows the foot that has been placed in a certain position to remain so, it does not fall back following its weight. That the *tibialis anticus* with its tendon appears more prominent, and that the position of the foot becomes one of adduction is readily noted, as well as that the *extensors of the toes* become tense. The muscular tension remains for some minutes and may become quite decided. For brevity's sake we have called this condition *foot tonus* in comparison to foot clonus.

There are also phenomena in the *course of the sympathetic*, the vasomotor fibres. Their irritability, independent of the degree of intoxication and rise in temperature (Trousseau's phenomenon), is very frequently present. Perhaps this is in connection with the fact that *circumscribed edema* as well as *erythema* may appear as rapidly as they disappear. This even becomes conspicuous to those about the patient.

Sensation is often altered, sooner diminished than increased, but not in all of its qualities; whether this is due to central or peripheral causes cannot be determined.

The same is true of *neuralgia*. This sometimes introduces the affection in a *typical manner*, apparently even existing as a substantive affection for some time, then the general affection follows, perhaps with a lethal termination. But also in the later course of sepsis may neuralgias appear: *sciatica*, *brachial*, *intercostal* and *trigeminal neuralgias*—showing the usual points of localization. With this it may happen that the pain may jump from one nerve to another even to one quite distant. What I have seen is about as follows, that in spite of a *long duration*, the *condition did not become habitual*. This may be against the view that a *neuritis* is present.

The *nerve-trunks* may be affected by *true inflammation* if a phlegmon occurs in their course. Thus, I saw the pneumogastric and phrenic nerves, in their course through the mediastinum, embedded in a thick layer of pus.

Visceral neuralgias of the abdominal organs I have only met with exceptionally. *Angina pectoris* is due less to sepsis than to the other changes of the heart that occur in the early stages.

And now a word regarding the *organs of special sense*, especially the *eyes*.

Litten in his beautiful work¹ has shown the *great importance of examining the eyes by means of the ophthalmoscope*.

Among 35 cases twenty-eight times he found *changes in the fundus* of the eye, in each case *retinal hemorrhages*, but also five times *bilateral* and three times *unilateral panophthalmitis*. However, these frequent findings must not be looked upon as a general rule.

¹ Ueber septische Erkrankungen. Zeitschrift für klin. Medicin, Bd. ii, p. 378 ff. (1881).

Litten's material embraced the severest forms, especially the puerperal variety, and this is a group which retains its peculiarity by the severity of the infection. This primarily explains the frequency of hemorrhages; also the panophthalmitis, which we might be inclined to refer to the entrance of emboli from the heart attacked by endocarditis, according to Litten's experiences, does not appear to follow. That they might occur in this manner cannot be questioned.

It is positive, therefore, that, even if everything is included in the least number of cases, only a certain result can be obtained by the ophthalmoscope. Of great value (Romberg) is the fact that in about one quarter of the cases of malignant endocarditis retinal hemorrhages are found.

It must be remembered that the "*septic retinal changes*" as Eversbusch¹ calls them, by no means lead to a destruction of the eye, neither do they indicate a bad prognosis.

As often as the *middle ear* is the starting-point of sepsis, as rarely do diseases in this organ occur in a general infection. I have only heard of one case which one of my colleagues, Wagenhäuser, diagnosticated, in which an exudate in the tympanic cavity was found to be present.

In what manner it occurs that *nutrition* and the *condition of strength* suffer so severely in septic diseases is not known. Exact investigations regarding metabolism are not at hand.

Regarding alterations of the blood, several things are known. E. Grawitz² has concerned himself with this study. The *chief findings* are the following:

The *blood* increases in watery constituents, decreasing in *solids*, this concerns the serum as well as the erythrocytes. The *leukocytes* may increase and this occurs in the majority of cases. *But this is by no means constant.* Grawitz remarks, "*that not rarely active inflammatory processes with pus-formation may be present without leukocytosis occurring.*"

DIAGNOSIS

We now come to the diagnosis, and I must designate the points of support which are concerned in sepsis in comparison with other diseases. But with these I shall mention *my own mistakes* in diagnosis as I have profited most from them.

What *primarily raises the suspicion of the possibility of sepsis?*

A preceding puerperium, a deep wound naturally. But we must not content ourselves with this. It has been shown that slight injury to the skin or mucous membrane is sufficient to permit pus cocci to enter, and this not necessarily at the point at which it occurred, to produce inflammation. It must not be forgotten what an angina may mean. Inflammatory processes of the middle ear must be regarded, and cicatrices that have been healed for a long time must be investigated. The heart must be examined, even if no symptoms or signs are referable to this organ and disturbances which are caused by it are denied. The example of such a rapidly fatal course of sepsis

¹ In *Penzoldt und Stintzing*, Handbuch der Therapie innerer Krankheiten, Bd. i, pp. 656-657 der 3te Aufl.

² *Klinische Pathologie des Blutes*. 2te Aufl., Berlin, Enslin, 1902, p. 553 ff., containing complete literature.

(Observation VI) as I reported, shows the possibility that this is good practice. And in questioning the patient regarding his previous life, the conditions which are collectively called "rheumatism" should be accurately investigated. It may be that a case of mild sepsis may conceal itself under this name.

Then the *examination* must include all parts of the body that I have named as being the primary seat of the affection, and all those minute details to which I have called attention must be investigated. It is true they are small points, but they gain in importance by the fact that so many of them occur simultaneously.

If the signs of local disease do not become more prominent, then the *temperature curve*, the apparently *unaccountable high respiratory frequency*, its relation to the frequency of the pulse, give further, but by no means certain points of support. *Actual pathognomonic symptoms are not known to us.* At the onset of the disease—in case of a severe infection—the *determination of pus cocci in the blood* will probably show itself negative.

Formerly it appeared as if the attempt to detect microorganisms in the blood would have to be given up, for my colleagues, who were expert in these investigations, found nothing in the blood in cases which at the autopsy showed large colonies in various organs. Now the methods have changed: large quantities of blood are taken, at least a few cubic centimetres, and cultures are made with the most varied media. *In this manner microbes may be determined in the majority of cases. But not always;* it is, therefore, advisable not to be content with a negative result, but to repeat the investigation. Only after nothing is found again and again does the probability that pus cocci are not present become great. But there is no certainty, for they may be present in the tissues and not necessarily emigrate from them. The *soluble toxins* are more readily taken up in the general circulation, and they alone may produce the symptoms of the septic infection.

The *inoculation of the blood into animals* must be judged from the same point of view. As we do not know which microorganism is active in the given case, it is advisable to inoculate different species of animals, as not all of them are alike susceptible to the different cocci.

The *clinical picture* now develops further, it is rarely characteristic and I shall only briefly repeat the symptoms which may show themselves.

The decline in nutrition and strength is very marked, one might almost say occurring under the eyes of the observers; in the severest cases and also in the mildest it is such that it becomes conspicuous in comparison to the demonstrable symptoms. *Marked sensations of severe illness.* *Fever* in the form of actual intermitting attacks accompanied by chills, then more or less remitting in character, sometimes being almost of a continued type, then again showing irregular temperature, being distributed over the twenty-four hours; longer afebrile periods are included.

Manifold *phenomena on the part of the heart:*

Upon the whole *asthenia with increased irritability.* Irregularity in the strength and sequence of the individual pulsation, cyanosis, coldness of the parts distant from the heart, the hands, the feet, the ears, the nose. At various times demonstrable inflammations of the heart and its membranes.

Increase of the *respiratory frequency*, even if no signs of local disturbance can be demonstrated in the respiratory organs. Very often *circumscribed catarrh of the bronchi, areas of consolidation in the lungs*, appearing and disappearing rapidly; if they are of gross embolic origin they remain and develop, this being due to the nature of the embolus. In connection with the pulmonary foci much more frequently than as an individual affection, *effusions into the pleura* varying in quantity and in composition.

Inflammatory foci in or around *the bones*, circumscribed, so that the adjacent parts are free, subject to great variations, disappearing as rapidly as they have appeared. The periosteum in these areas sensitive to pressure, the cutaneous covering perhaps showing inflammatory edematous swelling and redness. From these most frequent, mild forms, transition into well-developed osteomyelitis. The long tubular bones most commonly affected, rarely the flat bones, those of the pelvis more frequently than those of the skull.

The joints, especially the large ones, show effusion or only their capsule and the surrounding soft parts are inflammatorily swollen. *The cutaneous coverings* slightly edematous and reddened or showing phlegmons which invade the soft parts deeply.—The exudates are serous but may also be purulent. *In a severe infection*—usually, however, only in the puerperal form, or arising from other trauma—an *ichorous condition with complete destruction*.

Although the joints themselves are but slightly attacked, *tenderness of the bone upon pressure in an area outside of the capsule along the shaft is not absent*. Then foci must be searched for in other bones.

Implication of the *skin* characterized by a *protean character*: hemorrhages of varied size and form; erythema, from roseola to erythema multiforme and erythema nodosum. Superficial pustules and vesicles, destructive inflammations which may invade the deeper tissues and distribute themselves widely, or they may be quite superficial, simulating the eruptions of scarlatina and measles.—Upon the visible *mucous membranes* now and then conditions resembling those upon the external skin.

The kidney and its pelvis attacked by inflammation; *albumin* dependent upon this being quite *regularly present in the urine*; almost always *severe headache*; in the severer cases phenomena due to *the brain and its meninges*, but more severe than in most acute infections; however, actual inflammations may also occur.

Of *general neuroses*, *chorea* is not rare but *catalepsy* may also be present.

Neuralgias of the most varied nerves, peculiar *disturbances of the cutaneous and tendon reflexes*, as well as *disturbances in the sensory nerves*.

Hemorrhages of *the retina*, circumscribed inflammatory foci, even panophthalmitis, are found.

The spleen is enlarged, but, on account of its softness, it is usually not palpable.

Constipation is the rule. Copious severe diarrhea is not rare in puerperal sepsis. In all severe septic infections *hemorrhages* from the bowel are possible.

If no *single organ* in particular calls attention to the affection, the attempt must be made to construct the diagnosis by asking the question: In what other diseases, due to the entrance of microorganisms, does it happen that individual parts of the body are affected the same as in the case in question?

For this may be the starting point: *Sepsis is certainly always distributed over a great part, probably almost entirely over the organism; "Seek, and ye shall find"*—is true in this instance.

But one fact must not be disregarded: *Are there other microbes which share certain peculiarities with pus cocci?* And may such peculiarities influence the diagnosis? This question must be answered in the affirmative. For *if we name the characteristic properties of pus cocci, we must emphasize: They are originators of inflammation*, they may settle in many organs and may usually, mostly paroxysmally, from time to time in great numbers and at long intervals, enter the circulation.

These peculiarities are common to *pneumococci* which, in fact, are closely related to pus cocci, but they are also common to the *tubercle bacillus*. These are the germs which are most likely, especially at the onset of the disease, to give rise to difficulties.

I believed for a long time *that the peculiar bone pain, which has been so frequently mentioned, was a somewhat characteristic and peculiar symptom*. But this is not true. As has frequently been noted, not a single case of pneumonia showed bone pains—this symptom was regularly searched for—yet, after many years there occurred three cases in the course of a few days (from February 19 to February 25, 1891). These cases showed well-developed disease of the bones including their periosteum, as in the case of sepsis, and also other symptoms which are frequent in the latter affection. I shall report one of the cases that terminated fatally.

OBSERVATION VII

Croupous pneumonia of the right and left lower lobes. In the right pleura a purulent exudate amounting to 600 cc. From the third day of the disease to the ninth well-developed sensitiveness upon pressure of the long tubular bones. Severe constitutional phenomena. Death upon the seventeenth day of the disease. Fränkel's diplococci, demonstrated microscopically, as well as by inoculation into rabbits (Prof. v. Baumgarten).

A gardener, aged thirty-four. After a previously existing catarrh which had improved somewhat, suddenly a severe affection beginning with chill. Eighteen hours later *a lesion in the right lower lobe* could be demonstrated.

After the temperature had fallen to 99.5° F., *a second chill* occurred twenty-two hours after the first one, the lesion had distributed itself and become more dense. Upon the following day resolution, crepitation beginning; the temperature again fell for a period to 99.7° F., rising toward evening to 105.8° F. The infiltration of the lung cleared somewhat in certain areas, in others it became more marked, this condition continuing for some time.

Upon the eighth day of the disease *the first signs of a right-sided pleurisy*, upon the thirteenth day *a beginning consolidation of the left lower lobe*. The entire process is characterized in that the patient complains of a marked sensation of weakness and decided debility is also distinctly visible. The general infection, much more than the focal disease, brings about the lethal termination.

There was found:

At least *three repeated invasions* of the poison, showing themselves by chills and rapid rises of 5½° F. in temperature in a few hours, as well as by vomiting. Probably renewed invasions occurred more frequently.

In the lobe of the right lung, which was earliest and most severely affected, the inflammation remained longest. The process was disseminated here from the eighth day of the disease, the development of a metapneumonic purulent effusion occurring in the right pleura.

The lesions of *the left lung* were only susceptible to physical examination upon the fourteenth day of the disease, probably they occurred earlier but developed no signs.

Sensitiveness upon pressure of the bones from the third to the ninth day of the disease; the left upper arm and both thighs were especially affected, in these regions slight pressure showed very painful foci.

The forehead, the left side of the nose, the left knee and the left cheek showed circumscribed areas which were erythematous and slightly swollen, followed in the next few days by slight desquamation. The remark was made upon the first examination of the patient that this erythema showed great similarity to sepsis.

Taking all into consideration, we are compelled to admit that a pneumococcus infection of this kind very closely resembles an infection due to pus cocci.

Both of the other cases, similar to the one just reported, showed many points of relation to sepsis.

OBSERVATION VIII

Croupous pneumonia. Primarily no distinct focal phenomena, only upon the fifth day of the disease consolidation of the left lower lobe was demonstrable. Two periods of invasion; severe pains in the bones from the onset, friction over the spleen, liver,

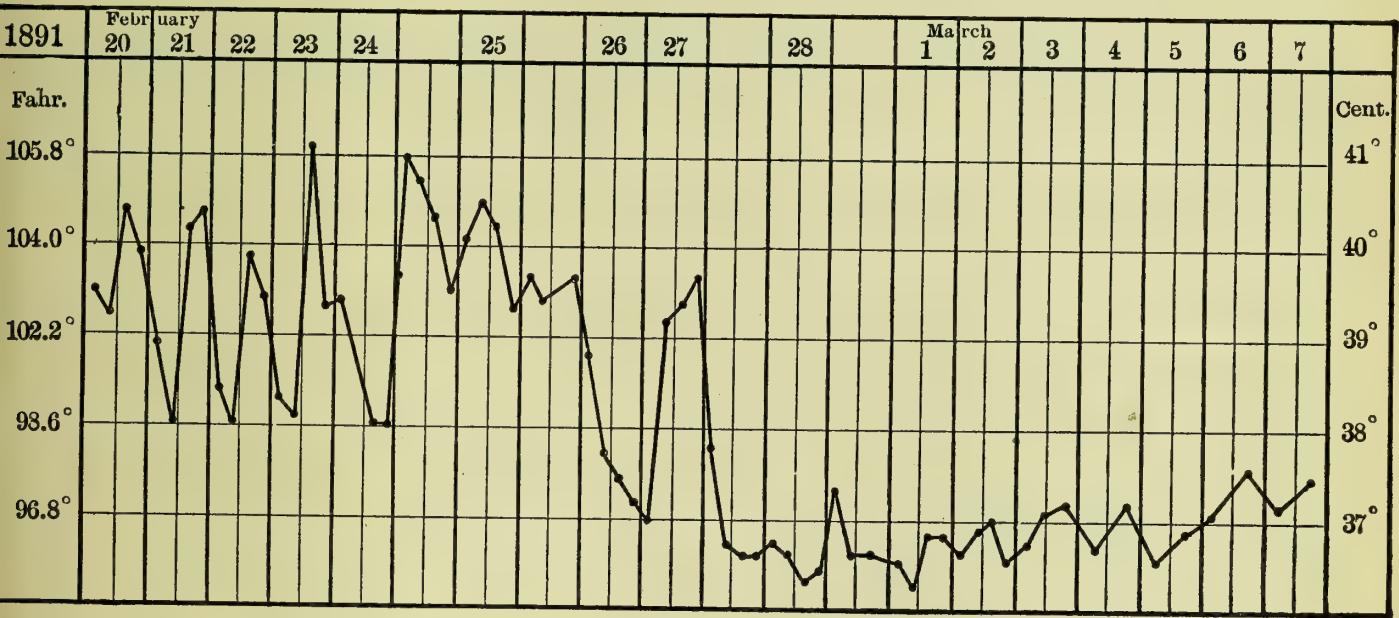


FIG. 48.

and at various areas of the thorax. Severe collapse upon the fifth day of the disease, defervescence by lysis from the sixth day of the disease—recovery.

A grape-gardener, aged twenty-one, previously healthy, was taken ill upon February 25, 1891, at half past nine in the morning, with sudden severe chill, treatment began upon the next day. Only diminution of vesicular respiration noted in the upper portion of the lungs upon both sides, but sensitiveness to pressure in the region of the eighth and ninth ribs in the axillary line, bilaterally in the region of the knee joint which is very sensitive to pressure, temperature 104.9° F., pulse 132, respirations 42.

Upon the morning—end of the second day of the disease—complete resolution, temperature 96.8° F., pulse 78, respirations 16. Patient gets out of bed, but, on account of chills accompanied by vomiting, is forced to return.

I will mention but briefly: focal phenomena in the lungs, indistinct at the apex, upon the fourth day marked, from the fifth day on distinct, later complete consolidation. Plentiful rusty sputum.

Bone pains upon the fourth day. In almost all bones, even upon slight pressure, upon the sixth day of the disease marked improvement and upon the eighth complete disappearance of this symptom. Splenic dulness increased from 8.5 by 6.0 cm. to 12.5 by 7 cm. Over the spleen, the liver, and at disseminated areas over the pleura, up to the eighth day of the disease, fine friction.

On the fifth day of the disease, in the evening *collapse*. Pulse 189, respirations 49, irregular cardiac activity, high grade of cyanosis. The cardiac asthenia so serious that the house physician remained at the bedside for four hours to watch the effect of the stimulants administered. The temperature was neither unusually high, nor did it rise. *Antipyretics were not administered*, only cold baths (twelve in all) which were always well borne. Cardiac action during the following two days still irregular, then rapid recovery so that the condition of the lungs became normal *on the twelfth day from the onset of the disease* and the patient was able to leave his bed.

I need only mention that the condition of the *heart*, added to the other symptoms, was calculated to increase the suspicion that sepsis was the underlying affection, especially as the nutrition and condition of strength of the patient had suffered severely.

If the temperature curve is observed (Fig. 48), which is that of the third case, an irregular rise and fall will be noted that but very rarely occurs in croupous pneumonia, followed by a rapid fall which is permanent.

OBSERVATION IX

A boy aged six, who was first treated for *varicella*, was attacked upon February 20th with pneumonia; for some days very indistinct local phenomena were present, then becoming distributed in the left lung, and diffused in all directions. *Bone pain* from the fourth day of the disease on.

In the *sputum* Fränkel's diplococci were present, but they were smaller than usual, and a rabbit inoculated with them remained alive. (Investigations by Prof. v. Baumgarten.)

From this it will be seen how very difficult it is to gain a correct insight into this affection. Observation VI may be taken as a type, apparently pneumonia, in fact streptococcus sepsis. I could further report cases in which the anatomical picture of a genuine pneumonia with endocarditis and meningitis was revealed by the autopsy, in which, however, it remained undecided whether pneumococci only, or also streptococci in connection with them, were the pathogenic agents. There is no good reason to decline the designation **pneumococcus** which is chosen by some investigators—or if the name is preferred, **diplococcus sepsis**. To recognize the affection by simple observation of the patient is impossible. Perhaps the demonstration of microbes from the blood or from some part that is diseased, as, for instance, the pleural exudate, may clear the situation. The *course* may be determining in so far as pneumococci in the human organism have a shorter life period, as a rule. If now in sepsis the phenomena improve during a brief period, with complete and permanent fall of the temperature to normal, diplococci may be thought of as the pathogenic agents.

The entrance of *tubercle bacilli* in such massive quantities that they produce a picture designated as *acute miliary tuberculosis* may present a clinical picture resembling sepsis. A widely distributed, severe *capillary bronchitis* which naturally gives a special character to miliary tuberculosis, I have not seen in sepsis, and this condition is of great importance in the differential diagnosis. If the *ophthalmoscope* reveals tubercles in the choroid, if hemorrhages or the peculiar changes of the retina are observed that occur in sepsis, the case is clear. But unfortunately how frequently are these conditions absent. And if miliary tuberculosis lasts for more than four weeks—and

this is by no means rare—when the serous membranes, the pleura, the pericardium, the meninges, the peritoneum are implicated, the similarity to sepsis becomes so considerable as to make a differentiation impossible. I have seen some, naturally but very few cases of that kind, but I was not able to follow them accurately enough to give a definite report regarding them. If endocarditis was previously present, this points to the possibility of sepsis, but it is no more than a probability. Vice versa, if tubercle focal diseases are present, this favors miliary tuberculosis.

If but *very few tubercles* are disseminated in the body, the symptoms produced by them may resemble those which occur from the presence of but *very few pus cocci*.

I refer here in particular to those collections upon the *endocardium* which produce but slight, and especially but very irregular, rises of temperature, now and then fine friction over the pleura, the spleen and other organs contained in the peritoneum. Now the same conditions, especially the irregularity in the course in the temperature curve, may be brought about by tubercle bacilli.

It is well known now that in a *completely developed pulmonary tuberculosis*, a *mixed infection* is present in which pus cocci make themselves prominent. *Streptococci* form the chief constituent of the "flora of the cavity," as the condition has been called, besides them there are harmless saphrophytes, and tubercle bacilli flourish very well side by side with both. It is, therefore, not remarkable if in the tubercular subject now and then symptoms arise which are not due to the tubercle bacillus. The *hectic fever* is attributed to streptococci, but accurate study would perhaps clear this confused picture in many directions.

Now a new difficulty arises: What about the *differentiation between sepsis and acute articular rheumatism*?

A question which is before the house at this time is this, whether or not acute rheumatism is due to a pathogenic agent belonging to the group of pus cocci, or at least closely related to them. This is not the place for a complete discussion of this question. I shall limit myself to the following: In Tübingen in the course of the last twenty years a form has developed which in many ways shows great similarity to acute articular rheumatism, but which does not markedly differ from the previously mentioned disease, as was formerly the case. I believe this affection to be due to a pathogenic agent which produces sepsis, and I diagnosticate *sepsis* if in the *typical clinical picture of the acute articular rheumatism*—I refer to the clear description which Senator¹ has given—*these deviations* appear:

1. *The joints*, although sensitive, show slight swelling; spontaneous drawing, boring and tearing pains, although never absent, are comparatively slight, never reaching the marked grade that occurs in acute articular rheumatism.

2. *The bones* almost without exception are implicated in the manner previously described.

3. *Sweating*, sudamina, are not as frequent, and especially not as well marked as is the rule in acute rheumatic fever.

¹ *Ziemssen's Handbuch d. spec. Pathologie.* 1879, xiii, 2te Aufl., p. 13 ff.

4. *Salicylic acid* and its preparations are capable occasionally of diminishing the pains and reducing the temperature somewhat, but a specific effect is completely absent (see Fig. 55).

To this should be added *friction sounds over the spleen and liver, various forms of eruption upon the skin*. Endocarditis, in fact *disease of the entire heart*, is very frequently present. This in itself would not prove much as this also occurs to the same extent and with the same frequency in articular rheumatism. The question is, however, open to discussion as to what may be the meaning if after a period of years a valve defect which had appeared in the previously mentioned symptoms becomes the starting point of general sepsis.

In many regions of Germany similar conditions have been observed and time will teach the connection between these pathological pictures and acute articular rheumatism.

Severe cases of *influenza* may give rise to diagnostic doubts. As gripe favors the settlement of pneumococci as well as of pus cocci to a high degree, mixed infections are often enough present. Whether they can constantly be definitely recognized has been variously answered; I have had no opportunity of forming my own opinion.

What about *enteric fever*, can this affection be confused with sepsis?

By many physicians, not alone the older ones, the name typhoid is used, especially in speaking to laymen, so that it includes every general affection running its course with distinct cerebral phenomena, with high fever, and long duration. In so far, severe septic infection may also be included in this group. However, true enteric fever, in its classical form, which in its systematic course furnishes the type, shows so great a regularity that confusion for the skilled observer would appear to be excluded. This is usually true. However, the examination of the points of support upon which the diagnosis is founded, will show that the individual symptom as such is much less determining than the periodic sequence of the other symptoms of the disease. This is especially true of the temperature curve. Any one of experience knows that a case of enteric fever which comes under treatment late in its course—after the third week—may give rise to great mistakes in diagnosis. I do not intend to discuss that at this place but I shall report briefly a case in which I made a *mistake in diagnosis*.

OBSERVATION X

Sudden onset of the disease after six weeks of malaise. Pains in the bones and muscles, irregular action of the heart, later dilatation. Irregular febrile course, great respiratory frequency without assignable cause, continued vomiting, constipation at first then diarrhea, intestinal hemorrhages. Death upon the sixteenth day of the disease.

Woman aged forty-two, admitted on November 28, 1895. Ill for six weeks, especially having pains in the small of the back; she was still, however, able to carry on her house work.

Upon November 25th *she was suddenly taken ill with vertigo and fever*; a shot was fired from the window in her immediate neighborhood.

Upon admission: Headache, lassitude, pains in the back and in the limbs, dryness in the mouth, and irritation producing cough. The muscles of the trunk, both upper arms and thighs, very painful upon pressure, the bones to a slighter extent, both the tibiæ and the cervical vertebræ. Heart not enlarged, impure sounds, slight irregularity also noted in the radial artery, slight bronchial catarrh, ileo-cecal region painful upon pressure. Spleen covered by intestine, not palpable.

During the next few days: Continued disturbances on the part of the heart, frequent vomiting, pain in the bones and muscles less marked but not absent. Up to December 1st (*sixth day of the disease*) continued constipation, followed by diarrhea, the stools not being characteristic.

Upon December 2d the spleen was palpable, fine friction being noted over the entire region. *Tinnitus aurium* (sixth day of the disease), and *difficulty in hearing*, added. *Cardiac dulness increasing*. In the left apex of the lung apparent development of a focus. Vomiting still continues. Upon the eleventh day of the disease intestinal hemorrhage and on this day albumin, many leukocytes and a large number of granular casts in the urine, some few red spots are noted upon the skin of the abdomen, upon the next day a few *petechiæ* appear.

The *intestinal hemorrhage* recurs after being absent for days, becoming exhausting, and being the *immediate cause of death* which took place upon December 11th. *Duration*, counted from the onset of the fever, *sixteen days*.

The *pain in the bones* and the *stubborn vomiting* continue up to the end. The *cardiac dulness* increased in extent.

The *autopsy* showed *enteric fever* in the stage of ulceration, erosion of a vessel in the course of a typhoid ulcer, medullary swelling of the mesenteric glands, parenchymatous degeneration of the kidneys and liver, parenchymatous

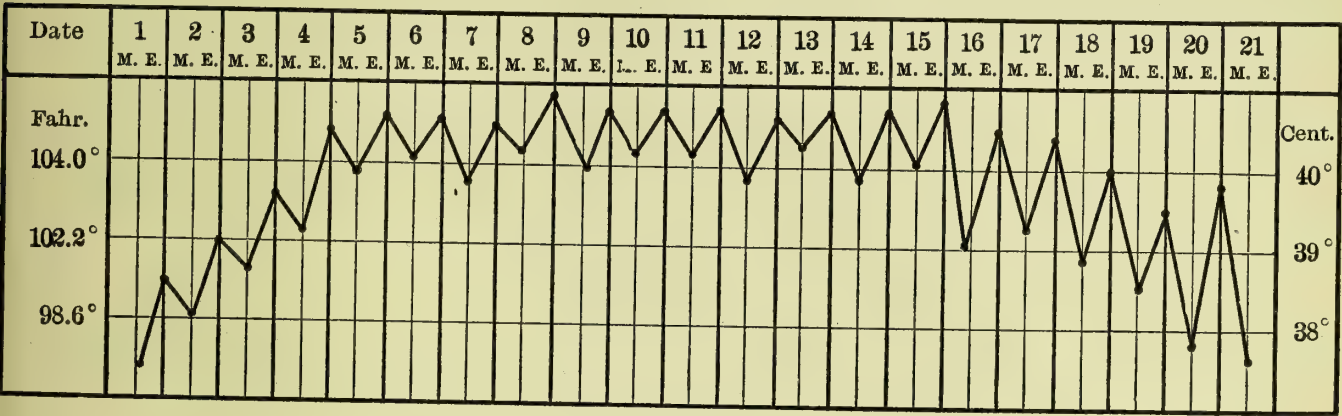


FIG. 49.

degeneration of the musculature of the heart, small fibrous deposits upon an aortic leaflet, small infarct of the left kidney (Prof. v. Baumgarten).

From the beginning I thought of the possibility that the disease was enteric fever and this was considered during the entire course of the disease.

Against enteric fever were the following:
A prodromal stage lasting six weeks, which is entirely too long, and the sudden, severe affection is also unusual. Still more, and this was the principal reason, the temperature curve.

The normal curve of enteric fever is shown in Fig. 49, and that of the case just described in Fig. 50. The variation in the temperature should also be considered (Fig. 51). Of special note are the days up to December 1st. This is an irregular course which rarely occurs in enteric fever, and it was not due to therapeutic measures. After the first intestinal hemorrhage (December 1st), we can no longer count upon a regular enteric fever curve, as the loss of blood brings down the temperature of the body. But even that cannot be primarily noted in this case, it shows a high fever, closely resembling an actual continued type. This irregularity lasts up to the termination of the affection.

Heart: Its labor somewhat disturbed from the onset, the pulse frequency too high for enteric fever. The *dilatation noted later* (increase of cardiac dulness) need not be considered, but that occurring upon the *sixth day of the disease is important*.

For a medium severe attack of enteric fever, this is too early, as was also the disturbed cardiac activity from the onset.

The *decidedly increased frequency in respiration* does not belong to the clinical picture of enteric fever, for which there was no explanation on the part of the respiratory passages nor of the lungs. The slight *catarrh* affecting the bronchi was present from the onset, therefore, rather against than in favor of enteric fever, in which, as a rule, bronchitis is earliest noted at the end of the first week.

The *albuminuria was too early and too severe*—from the third day—showing itself by the presence of large amounts of casts and leukocytes in the urine, characterizing *disease of the kidney*.

Enlargement of the spleen was of no importance in the differential diagnosis; as the investigation of this condition was difficult inside of the first few days, the time of the appearance of this sign could not be utilized as a diagnostic aid; the presence of friction is more in favor of sepsis.

The few *roseolar spots* were of no importance as they also occur in sepsis.

Of importance and *against enteric fever* was the *sensitiveness of the bones upon pressure*, which was certain from the onset up to the end of the affection. Of less importance, but, nevertheless, noteworthy, was the fact that the *muscles were so extraordinarily painful at this time*.

In favor of enteric fever were the symptoms on the part of the intestinal tract, naturally not those at the onset of the disease, for a stubborn constipation is not quite in favor of this view. *Sensitiveness upon pressure in the*

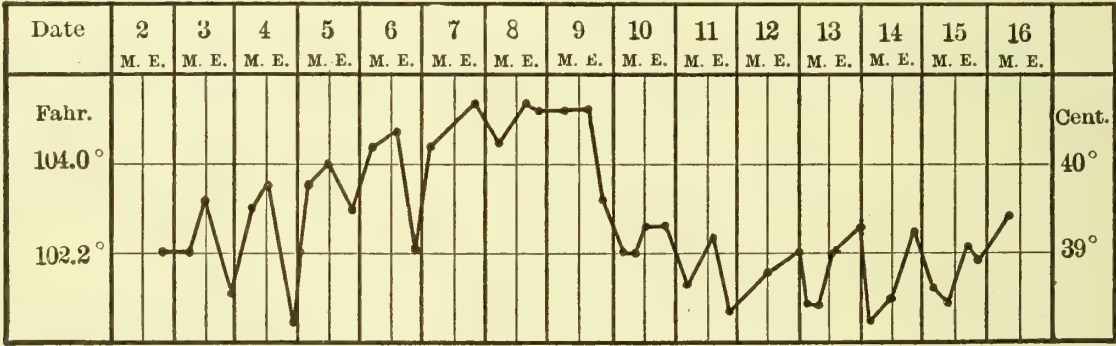


FIG. 50.

ileo-cecal region and *slight meteorism* now showed themselves (upon the third day of the disease)—again somewhat early—from the sixth day on, *diarrhea*, but no stools resembling pea-soup were present, and from the *eleventh day of the disease the hemorrhagic discharges* which were so detrimental to the patient. Regarding the time of the appearance of the hemorrhages, this corresponded well with enteric fever, and I became very suspicious.

However, as hemorrhages from the intestine also occur in sepsis and by no means in insignificant amounts, I adhered to my original diagnosis. The *difficulty in hearing*, a sign favoring enteric fever—formerly great value was

attached to this symptom—was combined with another symptom which was entirely against enteric fever, *the continuous uncontrollable vomiting*.

All in all, I believed septic infection to be the most likely diagnosis and only added enteric fever (?).

I could not avoid this error, nor do I believe now that I could have acted differently. Others may perhaps succeed; probably serum diagnosis (Gruber-

Date	Nov. 27	28	29	30	Dec. 1	2	3	4	5	6	7	8	9	10	11
8 A.M.		39.0	39.5	39.8	40.2	40.2	40.2	40.6	39.0	38.6	38.5	38.4	38.2	39.1	39.9
12 M.		39.5	39.8	40.0	40.4	40.5	40.6	40.6	39.0	38.9	38.8	38.4	38.3	38.9	39.9
6 P.M.	39.0	38.5	38.2	38.5	39.0	40.7	40.7	39.6	39.3	39.2	38.9	39.0	38.5	39.6	
10 P.M.						40.5	40.6	39.4	39.3	38.3	39.0	39.3	39.8	39.4	
4 A.M.						40.4	40.7	39.0	39.8	38.3	38.4	38.7	38.5	39.4	
Resp.		34	27			40	39	40	42	40	39	38	27	28	27
Pulse		111	120	120	124	142	140	147	137	129	123	132	117	129	126

FIG. 51.

Widal) may assist us in the difficulty, or the determination of typhoid bacilli in the urine, in which they have been found in very copious amounts, may show the true nature of the diagnosis.

Another error in diagnosis: *Cerebrospinal meningitis was diagnosticated*, and the case proved to be *streptococcus infection*.

OBSERVATION XI

Sudden onset with vomiting, headache, high fever, preceded by constipation, repeated vomiting, delirium, painfulness of the cervical vertebræ upon pressure, hyperesthesia of the skin. Death upon the sixth day of the disease with a temperature of 109.4° F.

Necropsy: Intense hyperemia of the brain and its membranes. *Endocarditis verrucosa valv. mitralis recurrens bacteritica. Embolic infarct and miliary abscesses in the kidneys. Streptococcus infection.* (Prof. v. Baumgarten.)

Girl aged eight. Two years previously had an attack of measles, from which there remained an inflammation of the cornea and a discharge from the ear for a long time.

During the night from June 21–22, 1900, *sudden illness* with vomiting, which repeated itself four times. In the course of June 22d, severe headache, fever and twice vomiting. Upon touching the child it became very restless and cried. Bowels constipated for a few days.

Admitted to the hospital on the morning of June 23d. Respiration 30, pulse 152, regular. General muscular unrest, especially noted in the face, pain, resistance and crying upon touching the child.

Bones: Only the bones of the left upper arm appeared to be sensitive on pressure. Consciousness retained, complains of headache, normal pupil reaction, decided diminution of the *patella reflexes*, *Achillo-tendon reflex* increased on both sides, more marked upon the left. Trousseau's sign marked. No disturbances on the part of the lungs nor of the heart, dulness being normal, the heart sounds pure, loud and regular.

Upon the 24th, *the patient is very apathetic*, in periods of brief intervals *loud crying*, repeated vomiting. *Great resistance upon touching the patient*. Upon the 25th, the same condition, only coma occurs, *feces and urine being involuntarily voided into the bed*.

Morphium hydrochlor. 0.003 is given hypodermically, followed by a quiet night. Upon the morning of the 26th *complete coma*. Right pupil dilated, reacting sluggishly, the left pupil normal. *Achillo-tendon reflex* increased upon the left side. Pressure upon the *cervical vertebræ* causes painful contraction of the muscles of the face. The

muscles of the nape of the neck are somewhat tense; resistance to touch less marked. *Pulse* still strong and regular. Upon the evening, morphia 0.0015 hypodermically. Upon the 27th, quiet night. The condition in the course of the day, with slight variation, very much like the previous one, only besides contractions of the nape of the neck, the muscles of the arms and legs also show this condition, and shortly before death become entirely stiff. *Lumbar puncture* gives about 30 cc. of a clear serum, but only transitorily brings back consciousness. *The temperature*, as will be noted in Fig. 52, rises by paroxysms until it reaches the hyperpyretic range of 109.4° F. Death occurs at this temperature.

This case showed such a well developed clinical picture of *infectious cerebral meningitis*—which occurs here in sporadic cases—that we were astonished by the findings at the autopsy.

That *the heart showed an old disease of the mitral valve*, no one suspected, nor could we suspect it. The report at the autopsy stated: “*Heart of normal size and shape,*” its activity up till the end showed no possible disturbance. Only the *microscopical examination* revealed that, in fact, an old endocarditis, however, a very slight one, was present, from which the recent streptococcus infection had found its point of origin.

Such mistakes in diagnosis are scarcely to be avoided. It is well known that the effect of intoxication in nearly all acute infections pro-

duces similar symptoms to those found in actual inflammation of the membranes and surface of the brain, so that an exact opinion is impossible. This case proves this in a decided manner.

I must now report another observation, from which it will be seen how treacherous pus cocci are.

OBSERVATION XII

Wry neck and difficulty in deglutition. Facial erysipelas of moderate extension, accompanied by a slight constitutional disturbance. After about three days, phenomena pointing to implication of the cerebral and spinal membranes, disturbance in the excretion of urine, marked nutritive disturbance, subnormal temperature, apathy. Death six days after the appearance of erysipelas.

Necropsy: Retropharyngeal abscess the size of a walnut, glomerular nephritis, general streptococcus infection (Prof. v. Baumgarten).

Girl aged seven and a half years, admitted February 6, 1890. Slight malaise few days previously, now pain on deglutition and on movements of the head. Redness, slight swelling of the soft palate, slight enlargement of the cervical glands. Gargle was ordered consisting of a 4 per cent. solution of potassium chlorate, and massage of the muscles which rapidly improved the condition, so that upon the eleventh day of the month the child was discharged. Upon the twelfth readmitted on account of facial erysipelas, upon the same day three thin fluid stools, no fever. The night between the thirteenth and fourteenth, delirium, upon the following morning apathy, marked vomiting, the child had suffered greatly in its nutrition. On the fifteenth, pains in the nape

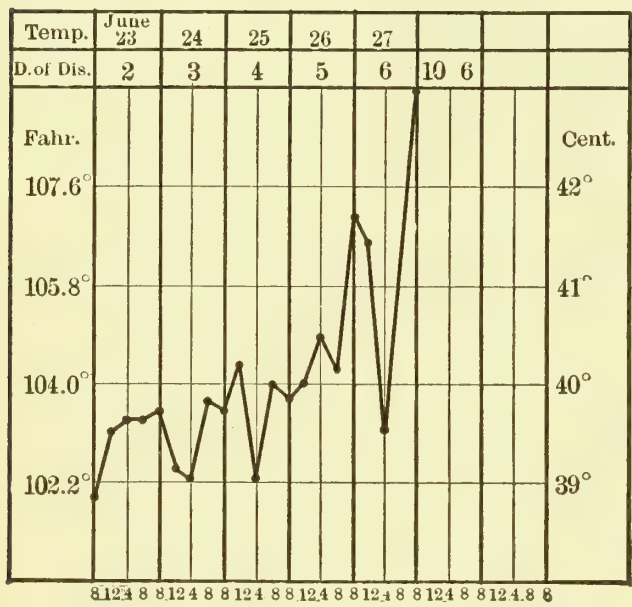


FIG. 52.

of the neck which, however, are not increased by movement of the head, with severe headache. "Head and back are held in a stiff position, the hands seek a firm point of support to limit the movements of the spinal column as much as possible." However, the neck and thorax are not sensitive upon palpation and pressure, but the two lowest lumbar vertebræ are sensitive to pressure both from the abdominal side as well as posteriorly. Cutaneous and tendon reflexes are more diminished upon the left side than upon the right. Dilated pupils not reacting to light. Pulse 63, irregular, regarding its strength, as well as in the succession of beats. Respiration very irregular, pauses amounting to ten seconds. Repeatedly, nausea and vomiting. Upon the sixteenth the apathy increases, death occurring upon the morning of the seventeenth. From the twelfth of the month on, the excretion of urine was diminished, it was only voided by drops or with the stool; it dripped from the bladder so that none could be obtained for examination even by means of a catheter.

That this was a *general streptococcus invasion*—they were cultivated from the blood—could not have been so easily suspected. It is true erysipelas was present, but it ran so harmless a course that no great importance was attached to it. It is, therefore, probable that the point of origin of the streptococcus invasion was the *pharynx*. "Upon the right wall of the pharynx laterally, slightly toward the posterior walls, but not quite extending to the median line, at the left of the second and the third cervical vertebræ, a *retropharyngeal abscess almost the size of a walnut*"—was mentioned in the autopsy report. At the onset this abscess probably gave rise to difficulty, but the symptoms were not those which would have

made it susceptible to diagnosis. Because the case was not assumed to be so severe, I only saw the patient once prior to death, and diagnosed a *meningitis upon a tubercular basis or a severe nephritis*, which, however, could not be demonstrated on account of the small amount of urine that could be obtained for examination. But against this was the *complete absence of anasarca*. It even remains questionable whether complete anuria was present

—the child had at least voided urine with the stool. The course of the temperature coincided best with the assumption of a tubercular affection of the cerebrospinal meninges. This can be seen from the observation of the temperature curve (Fig. 53), which even at the onset of the disease—the child was still well nourished—showed but a very brief rise in temperature (101.8° F.) in keeping with the mild implication of the pharynx and the muscular affection. Even the facial erysipelas only caused the temperature to rise to 101.5° F., subsequently up to the time of death *subnormal temperature* was present.

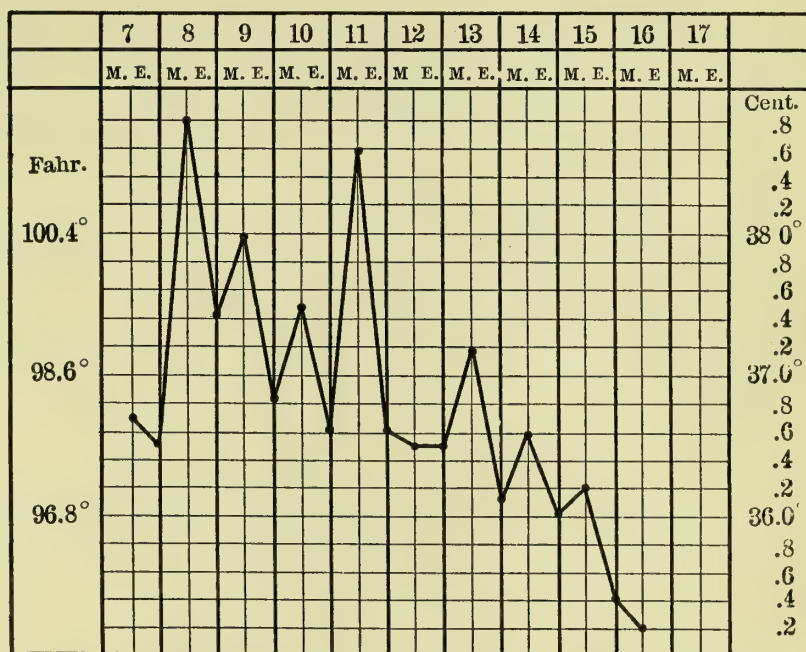


FIG. 53.

One point is taught by this case: *Streptococci need not necessarily produce decided fever.*

The **differential diagnosis** from *malaria* can only give rise to difficulty for a brief period. The demonstration of plasmodia in the blood protects us from error. Formerly we had to be content with a diagnosis *ex juvantibus*—larger doses of quinin, it is true, also clear the situation but, nevertheless, longer time is necessary. The temperature could only be utilized in those cases in which the simple types were present (quotidian, tertian, quartan). If we were dealing with duplicated attacks, etc., then nearly every septic fever might resemble malaria.

I must still report regarding the differential diagnosis from the *acute exanthemata*.

Erysipelas need not be considered; since we know that Fehleisen's coccus is a streptococcus, the question is answered.

Pustules resembling *variola* were seen by v. Leube.¹ This is a rare form of cutaneous implication in this infection, and the accompanying symptoms will guard against confusion. *Scarlatina* must be seriously considered, and especially *scarlatina in puerperio*.

It is well known that since Malfatti described an epidemic of malignant scarlatina which ravaged Vienna in 1799, scarlet fever has been looked upon as the evil spirit that brings death to the lying-in woman. I cannot enter into details here, but must refer to my historical and critical review of the subject.² It will be noted that although the *appearance of eruptions in septically infected lying-in women may resemble scarlatina throughout*, scarlatina differs in all other points markedly from "*puerperal scarlatina*." This disease is and remains a pure sepsis. The same is true of "*surgical scarlatina*."

It is good practice in diagnosis in the individual case in the acute exanthemata never to depend upon the appearance of the skin alone, but to carefully weigh all the other symptoms. If the last place is not assigned to the eruption many errors are liable to occur.

There are certainly many other opportunities by which sepsis may be confused with other diseases, but they are rarer than those already described. In the literature I find that Romberg³ from the Leipsic Clinic twice saw sepsis under the clinical picture of a *severe anemia—pseudoleukemia*—running a *fatal* course.

Still more confusing do septic infections become when they occur simultaneously with other diseases. And this is extraordinarily frequent. It need only be remembered that every injury of the covering membranes permits the entrance of pus cocci and that we do not know of a single pathogenic microbe, from the exclusive, aristocratic tubercle bacillus to the ordinary oïdium and decomposition fungus, with which they cannot flourish in combination.

¹ D. Archiv f. klin. Med., Bd. xxii, Fall iv, p. 255 ff.

² Jürgensen, Scharlach in Nothnagel's Handbuch, Bd. iv, ii, p. 16 ff.

³ Ebstein's Handbuch, Bd. i, p. 891.

PROGNOSIS

What course does sepsis run?

In general it may only be said: *Without any recognizable rule.* In the individual case there are certain points of support, thus the *cryptogenetic, fulminant affections*, which from the start show the stamp of well-developed intoxication, in a very brief time before distinct local foci occur, terminate fatally. There may be exceptions, however, they are very rare. By physicians who have studied sepsis arising from wounds and that form originating from the uterus, the same facts have been determined.

A rapid, favorable course, even in cases that appear mild, is not frequent. If the patients are closely observed even after an apparent recovery, frequent relapses are spoken of, but it would be more correct to say: Septic affection occurs in *paroxysms*, which are not only separated by days or by weeks but sometimes by months. And thus the case may drag on with intervals amounting to years.

The temperature should always be observed for a long time. It should be taken four times, at least three times during the day even slight deviations,

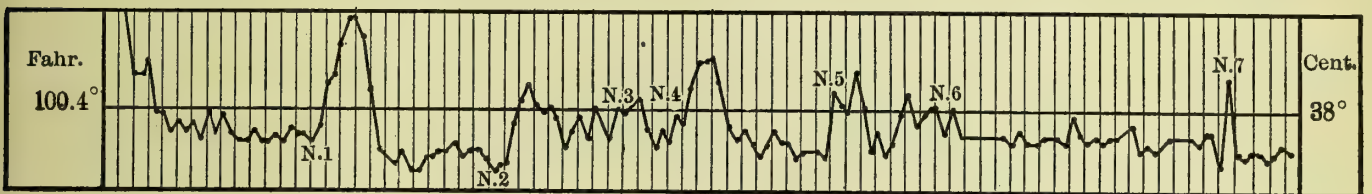


FIG. 54.

whether they be rises above the normal or irregular distribution of the temperature curve during the course of the day, *require full observation.* I have previously indicated what they point to in sepsis.¹ Usually with these changes in temperature, fresh local implication may be observed, but by no means always.

The temperature curve (Fig. 54) shows the *maximum of individual days* during a period of observation amounting to 187 days (from February 23d to July 30th). It was the case of a girl aged seventeen years in which the heart was markedly implicated. The figures at the different temperature rises indicate when and what disturbances coincided with them.

No. 1. Tightness of the chest, pain in the cardiac region and in the head, effusion and pain in the left knee joint, in the left tibio-tarsal articulation, pleural friction, angina. The menses occurred at the same time.

No. 2. The right and left shoulder joints painful.

No. 3. Pain and sensitiveness to pressure at the epiphyses of the left upper arm.

No. 4. Swelling of the right knee joint, sensitiveness of the femur upon pressure.

No. 5. Nothing determinable.

No. 6. Right humerus and radius sensitive to pressure, swelling of the wrist joint.

No. 7. Nothing determinable. Recovery.

Regarding the *localization* of the cocci of suppuration, I believe those in the endocardium to be the most dangerous; they show the greatest tendency

¹ See page 656.

to relapses, and if large quantities of pathogenic microbes are present upon the valves they are flooding into the circulating blood with all the consequences. Increasing implication of the musculature of the heart, which often enough goes hand in hand with endocarditis (pancarditis) favors the development of cardiac insufficiency.

I always give a very guarded prognosis. The paroxysmal course of the disease requires this. There is no certainty as to whether the apparent mild clinical picture may not suddenly change into a severe one. And we know less about whether a process, which to all appearance has run its course, may not break out anew. It is immaterial in regard to this question whether we are dealing with a re-infection or with the remains of germs—the fact of a new implication is not changed with this.

Sepsis in many respects shows *similarity to tuberculosis*: The possibility of a purely local and the general disease, the relapses from an old focus, to mention but a few points. Altogether, I regard *tuberculosis as the less serious microbic infection*.

The *periodic differences* in the character of epidemics which are common to all infectious diseases may also be plainly noted in sepsis. This must be taken into consideration when dealing with a large number of cases.

THERAPY

In cases which run a fulminant course, it is scarcely worth while to speak of treatment. The cases are invariably fatal and the physician must limit himself to not increasing the rapidity of the fatal issue. For this reason there are no drastic measures to be adopted, even if the temperature rises to the limit which in itself brings immediate danger. In these instances no antipyretic is of value, no withdrawal of heat, no matter how carried out, is of use. The disease in the individual organs, in these cases, may be treated, however, always with the proviso given above. But no one dare allow a patient septically infected, whose life is immediately threatened by an empyema, to perish without attempting to relieve the condition, for after the discharge of large quantities of pus a change for the better is sometimes observed.

An operative therapy should depend upon the opinion of the surgeon, and we should not hesitate to avail ourselves of such an assistance.

In treatment, the *fundamental law* in general is operative, *that the strength should be maintained and nutrition administered in every possible manner, with this the most careful nursing is of value.* This is not the place to enter into details; what is true of all infectious diseases is also true here.

However, one point must be emphasized with great distinctness: *The patient with sepsis must remain in bed for a long time. The thermometer gives distinct points of support for this.* I require the patient to remain in bed at least fourteen days after the last deviation from the normal, with continued control of the temperature. This is required for all local affections due to pus cocci, but especially for those on the part of the heart. I believe myself justified in assuming that a better, milder course is attained by this,

and that relapses are diminished and more readily prevented. More than once have I seen that *getting out of bed too early produced a new upflaring of the affection, which had not yet quite subsided, and that this resulted in death.*

Because I fear *every unnecessary movement* of the patient, I have not *made use of baths.*

In the severe cases nothing is attained by this, and in the mild cases in which marked remissions occur I believe an increase of temperature, in comparison to other symptoms, to be of slight importance. Water need not be feared, "taking cold" occurs as little here as in other diseases that go hand in hand with fever. *Cold sponging* is very grateful to those that sweat, and these washings may be even given at any degree of warmth which is grateful to the patient.

Neither do I fear a cold affusion in a warm bath, if a markedly distributed catarrh of the bronchial tubes indicates this treatment.

Large quantities of alcohol are recommended as a remedy to be regularly used in sepsis (for example by Romberg). I have not been able to note any influence, either for good or for evil, from this medication. I regularly give wine to fever patients, usually a light wine, but in septic affections of the heart I omit it, as it stimulates the heart unnecessarily.

The physician who invariably employs concentrated alcoholic drinks must observe one point: The fever patient does not very readily become intoxicated, nor are the evil consequences of the intoxication noted. But a fall in temperature, even of brief duration, often diminishes this tolerance to a decided extent. This must be observed in the marked remissions which sepsis manifests in its course, especially as disagreeable consequences upon the heart may show themselves.

The administration of quinin, similar to the alcohol therapy, has been handed down to us from former times. Both remedies are sometimes combined. Thus, Oskar Fraentzel administers two to three times daily 0.5–1.0 quinin, and not over 1.0 in an individual dose, with this 100 grams of a good, not too strong, red wine hourly. Even in malignant endocarditis he has seen good results from this treatment. I have to a greater and a greater extent become a doubter.

Salicylic acid and the salicylates, at least in the forms which run a course resembling acute articular rheumatism, are worth a trial. But this is constantly shown, that quite apart from their specific action which was always absent, only a very slight influence, even upon the temperature, was noted in the severe cases.

Thus, in this case: During three days 1 gram of sodium salicylate was given hourly. While the remedy was employed the hourly temperature showed 102° F. for twenty-eight hours; without the salt, 102.4° F. The temperature curve did not show decided changes (Fig. 55).

In mild cases the bone and joint pains, as a rule, diminish after the dose of salicylic acid. Aspirin—the acetic ester of salicylic acid—acts decidedly more mildly and appears to show the same good effect (1 gram four times daily).

Frequently the symptoms diminish after the administration of *phenacetin*— $\frac{1}{2}$ gram four times daily—which causes much less disagreeable after results.

Fall in temperature, as a rule, occurs, but this is uncertain. I never count upon it.

It is well to remember that, according to the experiences of the older physicians, it is good practice *not to stop the diarrheas* unless by their massiveness they become immediately dangerous. It is quite likely that toxins may be eliminated from the body in this way, and the change for the better which has not infrequently been observed after marked diarrhea may be explained in this manner. But this does not mean that by means of drastic purgatives similar conditions are obtained. Of the therapeutic results which are at-

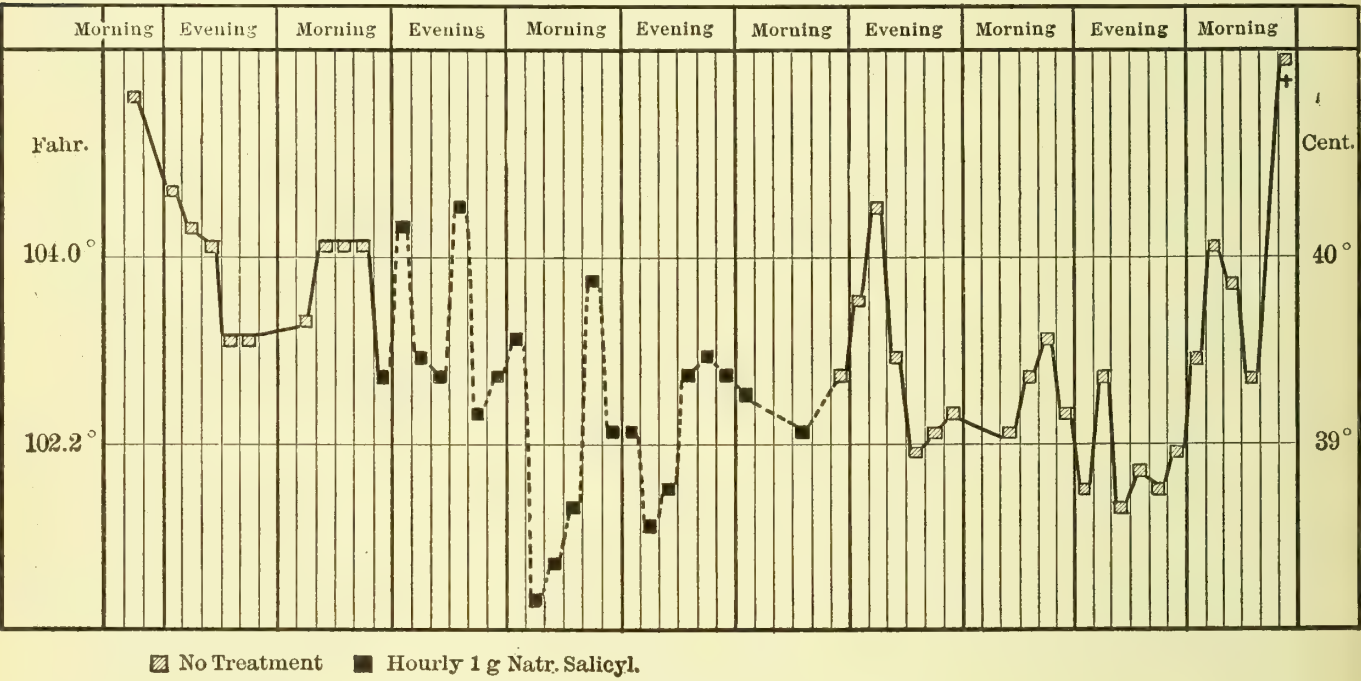


FIG. 55.

tained by calomel and jalap, which are administered in by no means small doses, after which improvement occurs, I only know from the reports of gynecologists. In puerperal sepsis this was practised by the School in Prague (Bohemia). Others, such as my old teacher and friend Litzmann, who was a pupil of Krukenberg and practised his teachings, was not partial to this treatment and in his last years he was decidedly averse to it. It appears to me that the majority of physicians hold the same view.

I hope that other physicians may find more satisfaction in the treatment of septic diseases than I have. It is possible that a curative serum may be discovered which may bring this about. The one advised by Marmorek was not effective, although it was only used for erysipelas, in which there is but one uniform causative pathogenic agent, Fehleisen's streptococcus.

[See also Serum Therapy, page 909.]

DYSENTERY AND AMEBA ENTERITIS

By G. HOPPE-SEYLER, KIEL

DYSENTERY

By dysentery, an affection known for a long time has been designated, in which the chief symptom consists in frequent fecal evacuations.

Later, in various ways, the attempt was made to limit this conception, for it was seen that the symptom previously mentioned did not permit the recognition of a uniform disease. Enteric fever, catarrh of the small intestine, etc., were separated and dysentery was declared to be a disease of the large intestine. More exact knowledge regarding the anatomical lesion, determined the fault to be a diphtheritic process of the mucous membrane of the large intestine and dysentery was mostly defined as diphtheria of the lower portions of the intestinal tract.

This purely anatomical definition could not be maintained from an etiological and clinical standpoint.

On the one hand, it was observed that in the epidemic appearance of dysentery the diphtheritic processes in the milder cases, which were unquestionably associated with the epidemic, did not appear; on the other hand, decided diphtheritic destruction of the intestine was found which was due to purely mechanical (constipation, foreign bodies) or chemical irritations (poisoning by mercury), which had nothing in common with infectious dysentery, a disease which appeared in epidemics or endemics. Thus, in uremia, the general intoxication of the body which develops from insufficient function of the kidney, producing diphtheria of the large intestine, only represents a part phenomenon of the general disturbance of the organism. Clinically, decided differences in the symptomatology and course of these diseases were noted from common dysentery, which was designated an infectious intestinal disease.

There then remained only such affections as pertain to true dysentery which had their seat, entirely or almost exclusively, in the large intestine presenting the distinct signs of being due to microorganism on account of their transmissibility and which were clinically characterized by the appearance of very frequent, usually small, mucous, bloody stools, often admixed with gangrenous shreds of mucous membrane.

In the last few years, however, this supposed clinical entity has been still further differentiated.

It was observed that the symptoms of dysentery varied in different epidemics; further it was especially shown that these dysentery-like maladies, particularly in the form in which they appeared in the tropics and in sub-tropical countries, ran a different course and presented characteristic complications which were missing in epidemic dysentery of the temperate zones

and in many respects showed anatomical lesions which were of a different variety.

Etiological investigation especially contributed to the separation of the individual forms of disease of the large intestine, and it appears that we are very near the goal of making our diagnosis with certainty by the proof of the pathogenic agent in the dejecta.

Above all, it has apparently succeeded in separating endemic tropical dysentery and sporadically arising diseases in other parts of the world which resemble it, from epidemic dysentery of the temperate zone, by the proof that the former is particularly due to the presence of ameba, therefore protozoa, whereas the latter owes its origin to bacteria which are closely related to the coli bacillus. Therefore, tropical dysentery and certain pathological processes related to it which are widely distributed, appearing here and there in the temperate zone are differentiated as *ameba enteritis* from *true dysentery*.

To designate ameba enteritis simply as tropical dysentery is not proper; for we are not dealing with a disease limited to these regions, as recent observations show that intestinal affections occur not infrequently which are due to ameba even in cold countries. Naturally, these are not as malignant and are much less disseminated than the affections occurring in the tropics. We will see, farther on, that occasionally other varieties of protozoa, showing a slighter degree of virulence are concerned in these processes. In the main, however, they correspond clinically and anatomically with the tropical forms.

In bearing in mind this etiological and clinical separation which is justified from these standpoints, we shall first describe epidemic dysentery of the temperate zone and then enter upon a description of ameba enteritis.

ETIOLOGY

Epidemic Dysentery.—Epidemic dysentery, true dysentery has appeared in the form of a pestilence even in ancient times. It occurred particularly in the time of war among armies, if the soldiers were placed in poor quarters, were insufficiently nourished, huddled together, and did not observe proper cleanliness. During sieges this disease not rarely decimated besieger and besieged; it was transmitted to the inhabitants of the city and the country, and armies which traversed countries often deposited the germ of the affection in the quarters that they had previously inhabited.

In old Indian books this affection is mentioned. Herodotus and the medical authors of the ancient world report epidemics. Especially severe epidemics occurred in the middle ages in almost all countries of Europe, in the seventeenth and eighteenth centuries in England, France, Scandinavia, the countries bordering on the Mediterranean, and further also in North America. The wars of this period, the Napoleonic campaigns, the Crimean war, the North American civil war, and, finally, the Franco-German and the Russo-Turkish war, showed a high mortality from dysentery, so that the disease was often more dangerous to the armies than were the weapons of the enemy. Even now, many a veteran is still suffering from the results of dysentery which he had contracted in a campaign.

Famine appears to favor the appearance and distribution of dysentery.

A predisposing cause is probably poor food, the great uncleanness which exists at those times and the partaking of contaminated food.

Massing of persons in narrow, dirty confines, as occurs during the time of harvest, in building occupations, and in industrial works may favor the development of dysentery.

Epidemics occur particularly at the height of the summer and in autumn; although it is by no means clear what the cause of this may be, whether rapid change in temperature, or great heat, are principally concerned in this.

The affection is frequently carried by individuals from one place to another. This may occur particularly by harvest workmen, vagabonds, travelers, etc. Soldiers who have returned home from infected districts, persons who visit relatives or friends sick of dysentery, those who attend funerals of persons dying from dysentery, where frequently in the house in which the corpse may be kept food is partaken of, may transmit the disease, in that they are affected themselves or take with them clothing, food, or other materials from places in which dysentery has occurred, and bring them to others.

The *contagium* is contained in the dejecta of the sick.

The mucus and hemorrhagic masses which originate from the lower part of the intestine, house the contagious principle. This has been known for a long time, although it has been attempted to declare fruit and other food substances as the only cause of dysentery, or it has sometimes been assumed that the infection is general, and this only leading to a production of irritative substances in the liver and in the intestine. The eating of large quantities of fruit may increase the difficulty in a simultaneous affection and cases may be conceived in which the external parts of fruit being contaminated with contagious material have directly, by this means, brought about the disease. On the other hand, it has been observed that the use of fruit does not show an unfavorable action, on the contrary, rather producing a good influence on the health of the affected people. Thus, the army of Prince Henry of Hesse, in 1778 suffered greatly so long as it was present in Nimes in Bohemia, the diseases soon ceased when the army came to Leitmeritz, where the soldiers ate fruit in large quantities. Such removal of parts of armies has very frequently had a favorable effect, especially when they left narrow quarters in farmhouses, etc.; it has even been noted that a bivouac in the woods produced an improvement in the epidemic.

The dejecta may all the more readily lead to further infections, the closer the patients come in contact with other persons and the greater absence of cleanliness and proper nursing.

For this reason, the affection is seen to distribute itself particularly among the lower classes, in workmen's quarters; villages in which the poorer population live are particularly affected. If we read of the conditions existing not only among the servants but among some of the more well-to-do, it cannot be wondered at that no one in the household escapes from the disease. Very instructive are the descriptions of medical officers such as Bornträger and others, regarding epidemics of dysentery in Western Prussia and other regions. There, as well as in some districts of Westphalia, Posen and Upper Silesia, for the last few years the disease has existed constantly, giving rise to epidemics in different regions. Among the country population, for the most

part, all the inhabitants are huddled together in a narrow room. If there be a patient with dysentery in the house, he very frequently does not even have the bed to himself but must share it with others. On account of the rapid and frequent fecal evacuations, a contamination of the bed cannot be avoided. The anal region is scarcely cleansed. The dejecta are often directly emptied outside of the house, in the yard, etc., as privies and water-closets are not at hand. If the patient is nursed by the housewife she very frequently must make up the contaminated bed and empty the chamber which is often soiled around the border, without afterward cleansing her hands with soap and water; she wipes her hands casually upon her apron and then attends to her other household duties, prepares food, looks after the children, etc. Children affected by dysentery evacuate their feces in the room, this may also occur with adults. The cleansing of the floor of the room is usually but very superficial; it often happens that the feces are removed by a cloth, a broom, or similar material, which also serve other purposes. In cities the quarters of the workmen often show quite similar conditions, principally on account of the difficulty of housing; the people show an equal lack of education and have very like habits. This easily explains how the affection rapidly distributes itself from such a household, that visitors, neighbors, etc., readily transmit the disease.

In the over-crowded quarters of workmen, soldiers, etc., dysentery may distribute itself in a similar manner. The privies are often contaminated in a frightful manner, on account of the tenesmus of the dysenteric patients, and if they are negligent, they often contaminate the seat with their dejecta. The direct contamination of the anus with the infectious material is less important for the conveyance of the disease than the soiling of the fingers, by touching the seat, the cover, etc., of the privy.

Drinking water has also been looked upon as a carrier of the contagion, and not improperly; thus in a garrison, dysentery has been seen to affect only such persons as obtained their drinking water from a certain well, whereas all those remained free of the disease that used another well. Naturally, the further distribution is also due to direct transmission from person to person by aid of the dejecta. Especially, superficially situated wells, appear to favor this condition, those which only reach to a gravel-layer containing water, beneath which an impermeable layer (clay, etc.) is present, covered by a thin vegetable mould, containing large quantities of organic substances. In country districts the wells are usually not deep, insufficiently protected against the inflow of surface water; not infrequently can it be distinctly noted how the overflow from a house or a dung-heap empties directly into it. Now if these belong to a house in which dysentery is present, the water will contain the germs of the disease and thus very readily assist the further distribution of the affection. Sometimes the wells do not have a pump nor are they supplied by a bucket, but everyone brings his own vessel with him, lets it down into the well, and thus, if it comes in contact with the dejecta of dysentery patients, infects the rest of the water contained in the well.

Flies which come in contact with feces thence resting upon other things in the house and surroundings, coming in contact with food, milk, etc., may

transmit the disease. During the warm summer and autumn they are present in plentiful amounts in houses of the poorer population.

In dysentery we find, in the main, analogous conditions as in enteric fever and cholera, only in the case of dysentery does it appear that the direct transmission of the diseased product from person to person in the manner previously described is important, whereas the infection by water appears to play a minor rôle.

In the last few years the attempt has been made to find the *specific cause* of epidemic dysentery. The entire clinical picture and anatomical course of the disease as well as its manner of distribution point to the fact that the exciting cause must be a bacterial microorganism.

The bacilli, which were previously found by Klebs, Orth and Ziegler, in Lieberkühn's follicles could not be definitely specified. Numerous investigators such as Babes, Maggiora, Bertrand, de Silvestri, Celli and Fiocca, Laveran, and others, found bacterial mixtures in which usually coli bacilli were predominant; with this the proteus, streptococci, staphylococci, etc., were also present. These authors are partly of the opinion that in dysentery a distinct kind of bacterial association is present; definite conclusions, however, cannot be gathered from their investigations. Of especial importance are the observations of Ogata and Shiga. Ogata found, in epidemic dysentery in Japan, in the mucus of the feces, bacilli enclosed in cells, as thick but only a quarter as long as tubercle bacilli. Shiga also isolated a bacillus resembling the coli bacillus in Japanese dysentery which did not produce fermentation of sugar and was agglutinated by the serum of dysentery patients. [Shiga¹ reports the following conclusions from his studies of epidemic dysentery in Japan: (1) *Bacillus dysenteriae* is constantly present in cases of dysentery; (2) it occurs only in cases of dysentery, never in healthy individuals or in patients suffering from other diseases; (3) the presence of the bacillus in the dejecta constantly attends the morbid process; (4) the bacillus is found almost entirely in the deeper layers of the intestinal wall; (5) the bacillus or its toxins have a tendency to produce hemorrhage; (6) the bacillus of dysentery exhibits agglutination-phenomena only with the blood of patients suffering from dysentery, not with the blood of healthy individuals or patients suffering from other diseases; (7) the property of producing agglutination varies according to the stage of the disease, being rapidly developed and reaching its highest point just before convalescence; (8) dead cultures of the bacillus, when injected subcutaneously into healthy individuals gives rise to marked local inflammatory infiltrations, the reaction being much less virulent in patients recovering from the disease; (9) Pfeiffer's reaction of the dysentery bacillus is especially marked during the convalescence of the patient; (10) the immune serum produces both prophylactic and therapeutic effects.—Ed.] Similar bacilli were confirmed by Celli, and further by Galli-Valerio. Pothien looks upon short, sometimes bent, sometimes straight, rods often arranged in threads (streptothrix) as the cause of dysentery and Escherich who investigated a house epidemic of dysentery in a children's hospital refers the cause to coli bacilli. It is certainly questionable, whether these catarrhs

¹ Deut. med. Woch., November 7, 1901.

of the colon which resemble dysentery have anything in common with true dysentery. Ascher, who examined feces from dysentery cases sent to him from Eastern and Western Prussia, could not discover characteristic bacilli, on the other hand, he regularly found a peculiar streptococcus. Such researches, if they are not carried on with fresh material, are always of questionable value.

Lately Kruse described a dysentery epidemic in Laar; he found, like all other investigators, who have busied themselves with the investigation of dysentery that only rarely and transitorily were ameba present, as an accidental finding in the feces, on the other hand, characteristic, plump rods were regularly noted in recent cases. These were found contained in pus corpuscles which formed purulent masses in the glassy mucus of the dejecta. They did not ferment in grape-sugar agar, they were thick, immotile and did not stain according to Gram. With the serum of dysentery patients, in whom the disease existed for more than seven days, in a dilution of 1:50, sometimes in much higher grades of dilution, agglutination took place, whereas the serum of healthy persons showed itself inactive. In persons who had recovered from an attack of dysentery the serum still retained the agglutinating properties with this bacillus even after one year. In advanced cases of dysentery in which there was a decided odor of decomposition in the feces, there was a mixture of numerous bacteria, which had overpowered the bacilli previously described. The pathogenic agent of dysentery would, therefore, resemble on the one hand, the typhoid bacillus, and on the other hand the coli bacillus, however, differing from each in some very important points (immotility, absence of sugar-fermentation, appearance of the culture, etc.). Animal experiments did not give a positive result, but this is also true of the typhoid bacillus, therefore, on account of the negative results of the animal experiment, the pathogenicity of Kruse's bacillus dare not be denied. The bacilli found in Japan differ from this bacillus, but in many respects show great similarity in their behavior.

Individual dysentery epidemics show decided differences in their course and in their clinical picture. It is, therefore, possible that the same pathogenic agents are not always present in these cases. If all the different bacteria are considered, it may be assumed that they vary but very slightly from one another. Changeable virulence and the simultaneous presence of other bacteria are also perhaps responsible for this condition.

PATHOLOGICAL ANATOMY

The anatomical changes are apparently slightly different in individual epidemics. Occasionally diphtheritic processes are particularly described, at other times, simple inflammation of the mucous membrane, with suppuration of the follicles and an undermining of the submucosa. These variations occur in individual epidemics, side by side, and not rarely does the colon show catarrhal, diphtheritic and putrid processes at the same time. It is not, therefore, possible to differentiate a diphtheritic from a catarrhal or gangrenous variety. Clinically, naturally, especially in regard to the prognosis, a decided difference is to be made between a mucus dysentery showing but

slight hemorrhagic tinges, and a form in which putrid, gangrenous shreds are passed in the feces.

In mild cases the mucous membrane only shows a hyperemia in the mucosa and the submucosa. The intestine is covered with mucus, which after washing, shows intense redness at the top of the folds and also between these more marked areas of hyperemia; it is thickened and for this reason more reddened over the overlying non-swollen tissues. The entire intestinal wall often appears more rigid, the lumen often decidedly narrow. The epithelium of Lieberkühn's follicles is swollen and turbid, between the tubules of the glands and in the submucosa there is hyperemia and edema with a plentiful round-cell infiltration.

If the inflammation advances, superficial necrosis of the mucosa occurs; it is found covered with bran-like scales which consist of decomposed epithelial cells, mucus and pus corpuscles. The glandular cells have disappeared, dissolved into a necrotic mass which covers the mucous membrane; at most, the lower part of the glandular layer is still retained, showing, however, greatly altered cells, in the process of destruction. Infiltration with round cells is still more marked in the submucosa. The cells particularly collect in the surroundings of the follicles, necrosis occurs in the same, they are desquamated by the muscularis mucosæ which covers them or they are noted as small necrotic plugs in deep grooves. The upper surface then appears yellowish-red or reddish, irregular bluish-red islands are found upon it. These latter correspond to remains of the mucosa whereas in other areas the submucosa is bare. Around the destroyed follicles the mucous membrane is often retained, for some time, as a small raised border. The follicular ulceration may now go more deeply, destroying the muscularis, even reaching the serous layer. Recovery often takes place in this stage of the disease. Flat cicatrices remain which may be covered again with epithelium from the still retained islands of the mucous membrane, but they do not show glandular development.

Frequently, however, widely distributed necrosis of the mucous membrane with development of fibrinous exudates in the connective tissue occurs, and deposits of croupous pseudo-membranes upon the mucosa appear. The intestinal wall becomes more thickened, the necrotic particles are stained greenish, brownish and black. The gangrenous destruction enters the muscularis and may even reach the serosa. Besides this, deep follicular ulcers, purulent decomposition of the submucosa, which often further on undermines the mucous membrane, and upon pressure at various areas, permits pus to appear as from a sieve, are found. Thus, we see a very varying picture in most cases which come to autopsy in that the disease, from the cecum downward, in an irregular manner, has altered the intestinal mucous membrane.

From the onset, in severe cases a diffuse, deep-reaching necrosis with fibrinous exudation appears, that is, a widely disseminated coagulation necrosis of the mucous membrane. In this form of diphtheritic, gangrenous dysentery, the bowel is already greatly thickened externally and rigid; it has a bluish appearance showing great filling of the vessels of the serosa. The lumen is narrow, usually containing only a thin, reddish fluid. The inner surface of the mucous membrane in its entire course from the cecum to the rectum is changed into a coarse mass, of a very bright color, offering decided

resistance to the scissors. Rigid folds of a reddish-white color cover it, between these there appear black and dark red areas. This is due to the fact that the muscularis is widened, laid in folds, and the submucosa and mucosa over it are changed into a rigid, homogeneous tissue, which is stained in various ways by extravasations of blood. Only in part may the remains of glandular tubules with epithelium be found which show coagulation necrosis. Between and beneath, the main masses show a trabecular reticulum of a fibrinous substance permeated with pus corpuscles and erythrocytes. The submucosa, particularly, often reveals large hemorrhagic spaces, these dilate it as well as the fibrinous exudation. The patients die before gangrenous destruction and desquamation of these masses occur.

If dysentery becomes chronic, deep ulcers and submucous fistulous passages remain for a long time; cicatrices of greater or lesser decided thickness and extent form.

If recovery occurs in dysentery, in which deep necrotic changes of the mucous membrane have taken place, the undermined mucosa often unites again, the superficial defects become smooth; deep ulceration in which decided necrosis of the mucous membrane has appeared is covered by granulations and produces marked cicatrices, which often narrow the lumen of the intestine in numerous areas. The submucosa is then generally permeated by fibrinous connective tissue, the muscularis also shows connective tissue threads. Remains of infiltration with round cells may still be frequently seen. The glands have disappeared in large areas of the intestine, remains of them have sometimes been changed into cysts, as the result of narrowing by constricting scar-tissue. A widely distributed rigidity and narrowing of the intestine appears, as well as atrophy of the glandular coat, and from this the decided disturbance of function of the large intestine may be explained.

Regarding the *changes in other organs*, these are of decidedly less importance. The upper portions of the digestive tract, from the mouth to the ileo-cecal valve, usually show the signs of catarrh. The peritoneum around the colon is sometimes slightly inflamed and injected. In severe cases, with deep necrosis and suppuration in the wall of the intestine, fibrinous exudation occurs, even purulent peritonitis; perforations into the free abdominal cavity are rare. The mesenteric glands are usually swollen, hyperemic, rarely purulent. In the liver, changes are usually absent, only rarely in the case of deep purulent ulcers, does pyelephlebitis and multiple pyemic pus foci appear in the liver. Then the signs of a widely distributed septicopyemia appear in the rest of the body. The spleen is usually small. The kidneys show hyperemia, in chronic dysentery sometimes parenchymatous inflammation. The heart is mostly flaccid; the entire organism shows the signs of anemia and cachexia.

SYMPTOMS AND COURSE

Regarding the *period of incubation*, this is variously given, and probably also differs in many cases; it is usually assumed to be about a week, but it appears that particularly severe affections have a shorter period of latency.

The onset is commonly insidious. Accompanied by slight colicky pains, lassitude, and other signs of ill health without fever generally occurring, the

condition of the bowels becomes irregular. Usually thin, but still fecal dejecta occur, more rarely is there constipation at the onset. In these stools, mucus of a glassy consistency and a yellowish color is found. The patient, as a rule, still follows his occupation, often believing that he is suffering from a transitory disturbance in digestion.

In from two to five days, however, the disease enters upon its severe stage. Frequently with phenomena of fever (chills and a sensation of heat), severe abdominal pains occur, in which the patients often almost double themselves; these attacks occur in paroxysms, the inclination to stool becomes so marked that the patient must give way to the sensation at once. No longer is a large quantity of thin fecal matter passed, but accompanied by decided burning and severe pain, which goes, hand in hand, with the contraction of the sphincter ani (tenesmus) radiating up the small of the back, only a small quantity of mucus is pressed from the bowel. This stool shows a bilious consistency, and frequently already streaks of blood. Microscopically, few epithelia and pus corpuscles are found. After a brief period this attack is repeated without the sensation in the meantime of having satisfied the inclination to have a movement. The patient believes, on account of the continuous irritative condition in the rectum, that fecal masses are present which must be emptied. Thus the attacks of tormina and tenesmus increase, in which but very small quantities, amounting to 1 to 2 tablespoonfuls, are evacuated. Ten to twenty in severe cases, even one hundred times during the day. In the morning, the sensation appears to cease, becoming more marked in the afternoon, reaching its acme in the night. The patient takes but little nourishment, partly from fear that it will give rise to peristalsis. He suffers greatly from thirst, the exertion, the pains, the mucus and hemorrhagic passages, which constantly increase in the next few days, and bring about exhaustion. The skin loses its turgescence, becomes pale, often yellowish, rarely icteroid, the bulbæ retract, dark circles surround the eyes, the tongue, the mucous membranes of the mouth and lips become dry. The urine is concentrated and irritates the bladder. By this means and in consequence of a transmission of the sphincter spasm of the anus to the neck of the bladder, strangury and ischuria occur, so that sometimes catheterization becomes necessary. The abdomen is mostly flat, not tympanitic, rather retracted; in the lateral aspect of the abdomen especially on the left side, the inflamed thickened colon is often felt as a tense elastic tube, sensitive to pressure. Sleepless, with irritating pains, the patient passes the nights. Vertigo, tinnitus aurium, headache appear. A moderate, usually remittent fever is only present in some of the cases. This is not unfavorable, if even occasionally higher ranges of temperature above 104° F. are reached. Much more serious is the tendency to subnormal temperature. The fecal movements in this advanced stage frequently appear like the washings of meat (*lotio carnea*), i. e., in a watery, slightly feculent fluid having a cadaverous smell, reddish or yellowish or slightly reddish fluid particles, the size of a pea or bean, usually red in color are found floating which frequently have the appearance of chopped meat. They do not consist of desquamated mucous membrane but only of tough mucus, which is pierced by red blood corpuscles, containing little white lumps composed of pus corpuscles, in the latter the characteristic pathogenic bac-

teria are principally found. Decided hemorrhagic passages may occur as the result of the erosion of a larger blood vessel. Granules resembling sago or frog spawn may appear in the dejecta which are either due to swollen starch from the food or consist of mucus, which perhaps has collected in the follicular ulcer.

After this condition has lasted for a few days, for a week or somewhat longer, improvement may occur and then the tendency to stool becomes slighter, the dejecta showing more of a fecal consistency. Then pappy or formed stools occur, but mucus and purulent masses are still adherent. Appetite improves, strength increases and the dejecta gradually lose their abnormal mixtures. Convalescence usually, however, lasts several weeks, and the intestine for a long time is sensitive to irritating ingesta, to refrigeration, etc.

In *the severe cases* after about a week the attacks of tormina and tenesmus diminish but they still disturb rest at night, the nutrition of the patient suffers greatly, the heart weakens, the pulse becomes small, the temperature often subnormal. The region about the anus is inflamed and excoriated, often prolapse of the rectum is present, which can only be brought back with decided difficulty causing great pain, thus the patients with increasing weakness, with a mind little or not at all disturbed, may die. But many may recover and the further course of the affection is then the previously described change into convalescence.

In *the severest cases*, which almost invariably run an unfavorable course (*putrid dysentery*), the feces passing during the paroxysms, which become severer and severer, are offensive, whereas up to that time they have only been insipid, lime-like. They contain besides very little fecal material and mucus particles, pus, as well as hemorrhagic, more or less decomposed, masses. They become greenish, brownish, or black, contain larger or smaller shreds which consist of desquamated, gangrenous mucous membrane. These must not be confused with the long rim-shaped tubular structures, which consist of compact mucus, as in membranous enteritis, and which may contain altered hemoglobin giving rise to the different colors. The patients emaciate rapidly, are apathetic, and finally, the putrid, watery contents of the bowel are emptied without the patient paying any attention to it. In consequence of paresis of the sphincter the eroded anus now remains open. Excoriations may now show themselves on the scrotum, penis, etc. Bed-sores occur. The pulse becomes very rapid, scarcely perceptible, the temperature subnormal; cold sweat covers the cold, moist or cyanotic skin. Lips and tongue are denuded, fissured, red, or covered with a blackish coat. The voice becomes hoarse. Hiccough and precordial anxiety appear and with or without alterations of the sensorium, the patient dies in collapse.

If in rare cases, in this stage, a cessation of the process still occurs the patient recovers but extremely slowly. The convalescence may last for months, and almost always decided disturbances in the large intestine remain as the result of cicatrices, stenosis, thickening of the gut and fibroid degeneration of the musculature.

In these severe cases, the impression of an intoxication is produced due to resorption of the products of decomposition, which are formed during the gangrenous destruction of the bowel. It appears that the bacilli of dysentery

themselves produce specific toxins (Celli and others). This would explain the disturbance in cardiac activity, the rapid loss of strength, and the occasional disturbances of consciousness, etc.

As **complications**, we occasionally note peritoneal phenomena. In a severe disturbance of the general condition they are not distinctly noticeable, in such cases the left side of the hypogastrium is very sensitive to pressure.

Further, the most varied changes occur as the result of septicopyemia, arthritic pains and swellings are not rare as well as muscular pains (rheumatic form).

In the mouth and in other mucous membranes, insufficient or faulty nursing may give rise to hemorrhages. Petechiæ, hematemesis, epistaxis, may appear.

Rarely is the liver the seat of abscesses, in contradistinction to the tropical form which is due to ameba.

Less often than in ameba enteritis does chronic invalidism occur in this form of the disease. In some cases, it is true, the patients recover but slowly, the stools for a longer period, now and then, are somewhat admixed with fluid or bloody particles, and pus may be discharged for some time with the dejecta. Then the intestine is very irritable. Food, difficult of digestion, or cold food produce colic and diarrhea; between these attacks there is a tendency to constipation due to a fibroid degeneration of the musculature as well as to cicatricial stenosis, especially in the region of the flexure of the colon, in the sigmoid flexure and in the rectum. With all this, however, the condition of strength and of the nutrition of the person affected, may be quite fair.

The **mortality** in individual epidemics varies greatly. There have been terrible epidemics, for example in North America, in which the greatest number of those attacked died; in Germany similar epidemics have occurred, in which a quarter of those attacked succumbed. In the main, it appears that dysentery has not only become much less frequent but also milder; for now as a usual thing the mortality only amounts to from 5 per cent. to 15 per cent. With an improvement in sanitation, the treatment of the patients in hospitals, and especially on account of the cleanliness and better mode of life of the lower classes, still further limitation of the affection is to be expected.

Death, as a rule, occurs during the course of the second week.

PROGNOSIS

The *prognosis* is unfavorable when offensive, gangrenous masses are mixed with the dejecta, when subnormal temperature and signs of cardiac weakness appear. Usually after these symptoms have been present for a few days, death occurs; if the condition lasts longer than a week, there is hope of recovery. In catarrhal dysentery in which only mucus is passed in the feces without gangrenous masses the prognosis is favorable. It becomes unfavorable when this condition lasts a longer time, in that a transition into the severe form or chronic changes in the intestine are to be feared.

DIAGNOSIS

The *diagnosis* in general is based upon the characteristic symptom-complex, the frequent tormina and tenesmus, the appearance of mucus and bloody stools, the small, frequent dejecta, and eventually the demonstration of desquamated necrotic particles of mucous membrane. It is to be hoped that it will be possible, with a more exact knowledge of the causative agent, to demonstrate its presence and by the agglutination test, etc., to make the diagnosis with certainty. The investigations of Kruse and others are very encouraging in this respect.

THERAPY

Prophylaxis is very important in times of epidemics of dysentery. Especially in the case of dysentery is there often opportunity to observe that State sanitation, proper treatment, care for the improvement in conditions of living, the removal of nuisances in regard to the manner of life, the proper supply of drinking water, etc., produce very favorable results.

If dysentery occurs in country districts or in quarters inhabited by workmen the patients should be removed from the unhygienic surroundings and placed in hospitals. The people must be instructed regarding proper care and measures that are to be taken to prevent the spread of the disease, especially cleanliness and disinfection of the beds. All materials that come in contact with the stools, the privies, especially their seats, dung-heaps, should be disinfected and care should be exercised that the overflow water and other effluvia do not get into the water-supply. For the nurses and those about the patients, water and soap must always be at hand. Best for this purpose are a lysol solution, carbolized water, corrosive sublimate and similar materials. Visits to patients, taking part in funerals, partaking of food and drink in infected places are to be prohibited. If dysentery occurs in garrisons, institutions, etc., in which there is a massing of people and if isolation or removal of the patient, disinfection and cleansing of the rooms and substances used by them, eventually the closing of suspicious wells do not produce results, all inmates should be transported to a different locality, for example, to dry open barracks, in tents, etc. This hinders the spread of the epidemic.

The importance of cleanliness, in regard to prophylaxis, is best seen from the fact, that physicians and trained nurses are rarely infected, whereas others frequently acquire the disease, who have only remained in an infected dwelling for a brief period, but who do not give the same attention to cleanliness which is practised by those of education, and particularly by those experienced in sanitary matters.

The *nutrition* is especially important in the severe cases. At the onset of the disease only mucilaginous soups (water gruel, barley water), bouillon, milk soup, with the addition of an egg to the soup, or ice water are to be given. The fluid is not to be cold as this increases peristalsis and produces tenesmus. Wine and other alcoholic drinks are not well borne, as a rule, they apparently irritate the intestine. The previously mentioned mucilaginous substances are best for fluid nourishment; weak tea also is grateful to the patient. During the early period, the patients usually take nourishment quite

well; if after a few days, decided intestinal irritation, with a marked loss of strength occurs, it is not necessary to stimulate at once; patients resist this, because the increase of nourishment increases intestinal movements and produces greater difficulty. Undiluted milk, at the height of the disease, is not so well borne as might be expected, it had better be diluted with tea, some effervescing mineral water, or like substances. Milk, especially in severe cases, often produces a sense of unpleasant pressure in the abdomen, even giving rise to vomiting. It is, however, advisable to use milk in the catarrhal form of the disease as it is such a valuable means of nourishment. Many patients will even take several litres a day. If the disease is protracted or rapid loss of strength occurs, concentrated food products must be used, of which we have a great quantity at our command, albumin preparations, tropon, plasmon, nutrose, somatose, meat extracts of various kinds, milk-surrogate, etc. These foods must always be given in small quantities, every two to three hours, and must be frequently changed, as the patient readily tires of them.

When tenesmus and diarrhea become less intense, soft boiled eggs may be given, scraped or chopped meat of fowl and fish, later beef, zwieback, crackers, toast, etc., and thus, gradually the ordinary food is taken; however, for a long time, spicy, sour and very fat food is prohibited.

The patient must remain in bed and be kept warm, the room should not be too cool, a temperature of from 68° F. to 70° F. is best, as the patient after satisfying the frequent tendency to defecation readily takes cold. Hot cloths, cataplasms, flax-seed poultices, etc., may be applied to the abdomen; they are very grateful to the patient and lessen tenesmus.

In severe cases a frequent change of the bed is useful, and a water-bed is very valuable. This has the advantage that the patient does not so readily acquire bed-sores, and in patients with subnormal temperature by filling the water-bed with water of a temperature of over 98° F. artificial heat may be applied; in the case of high fever, by substituting water of a lower temperature (from 68° F. to 77° F.) the patient may be cooled.

The anal region must be frequently cleansed and carefully dried with cloths or cotton, the excoriation covered with salve, containing boric acid or lead. Poultices containing aluminum acetate (2 per cent.) or lead water are often employed to advantage.

In the *treatment with drugs* we may often be inclined to give narcotics or sedatives, for example opium, to diminish peristalsis and tenesmus. Although this is attained for a brief period, the disturbances return later more markedly, giving rise to even greater difficulties. On the contrary, at the onset a *purgative* should be given, and castor oil has been employed with advantage. Rhubarb, senna, tamarind and other vegetable laxatives are less useful; they often produce severe colic and increase the difficulty. *Calomel* is especially valuable, from 3 to 5 grains should be given; if a green stool does not result in a few hours, the dose should be repeated. Calomel appears to have a deleterious effect upon the pathogenic agent, therefore not only to empty the bowel but also to inhibit the development of the germs of the disease. It may also be given in fractional doses, several times a day, continued for a longer period.

For a long time *ippecac* has been used, especially in tropical dysentery, ameba enteritis. Its use is also advised in epidemic dysentery. Formerly the root was given, from 15 to 30 grains in plenty of luke-warm water, so that vomiting should result. Now the attempt is made to avoid this, in that a hypodermic of morphia is given previously, or from 10 to 20 drops of tincture of opium are administered by mouth, and then from 15 to 60 grains of *ippecac* are given in divided doses. The patient must remain quiet in bed, a mustard plaster or counter irritant is applied to the epigastrium. Very little water, at best small pellets of ice, are employed to allay thirst. *Ipecac* is said to diminish tenesmus, to make the stools more copious, and to terminate the affection in a few days. In France, the administration of sodium sulphate, 15.0 grams in 150–200 cc. of water, given in one dose, followed in the next few days by smaller quantities, or a concentrated solution of magnesium sulphate with a few drops of sulphuric acid, are given in teaspoonful doses.

In the further treatment the use of *enemata* is particularly indicated. Naturally, it must be admitted that at most the lower parts of the colon are reached and these enemata are for the most part ejected rapidly, so that their use is often problematic.

Enemata of starch with tincture of opium lessen pain and spasm of the musculature. Starch is cooked in water so that it becomes of a thin, pappy consistence, 125 to 250 cc. are employed at a temperature of the body, 10 drops of tincture of opium are added and the entire amount is allowed to flow through a soft rubber tube, that has been well oiled and that is not too thick, and emptied into the intestine. The patient must make the attempt to retain the enemata as long as possible. If these enemata are employed at night, they will often give the patient the necessary rest.

To act upon the morbid process itself, astringent enemata have been employed. Small quantities of strong silver nitrate solution, tannin and alum solutions, have now been entirely abandoned. Now larger enemata, a litre or more, of a $\frac{1}{2}$ per cent. solution of tannin at the temperature of the body, are employed. The rectal tube is passed as high as possible in order to allow the fluid to reach the descending colon; the knee-elbow position is often useful for this purpose. Instead of the tannin solution a 1:100 solution of silver nitrate may be used, but this is without special advantage. Cantani uses this enteroclysis with some pressure at about a height of 2 yards. The fluid is said to reach the transverse colon. In acute dysentery this is hardly possible, as an enemata of but half a litre often produces unbearable pain, and in the case of deep ulcers and gangrenous processes this procedure may even be directly dangerous; it had better not be employed. In chronic dysentery, however, Cantani's method may be of value.

Enemata consisting of disinfecting substances, such as carbolic acid, corrosive sublimate, naphthol, creolin, boric acid, etc., are usually very irritating without being very useful; they may even produce symptoms of poisoning.

In severe dysentery, in which rapid loss of fluid occurs and the absorption of toxic products from the intestine damages the organism, the employment of an infusion of a normal salt solution will be very valuable, especially in those cases in which the patient takes but little fluid by the mouth. Accord-

ing to requirements, several times daily $\frac{1}{2}$ litre of a $\frac{3}{4}$ per cent. of sterilized salt solution, at the temperature of the body, should be injected subcutaneously, upon the inner side of the thigh or in the lateral portions of the trunk. In this manner the body is supplied with water.

Complications such as peritonitis, etc., are treated according to special indications. The sequelæ of severe dysentery in the colon and the tendency to a torpid action of the intestine produced by them, obstruction of the bowel, etc., are treated by the use of laxative mineral waters (Kissingen, Marienbad, etc.), by mechanical treatment (massage, gymnastics, exercise in the open air).

Convalescents should be sent to mild mountain regions if they do not recover sufficiently rapidly at home. Sea air appears to be less valuable for this purpose.

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[See also Serum Therapy, page 909.]

AMEBA ENTERITIS AND OTHER PROTOZOAL DISEASES OF THE INTESTINE

ETIOLOGY

THE so-called dysentery of the tropic and subtropical regions, which is endemic in these climates in numerous districts as well as many similar diseases occurring in colder regions is very often confounded with epidemic dysentery, the form which occurs particularly in the temperate climates. In all of these affections the colon is the main seat of the pathologic changes, and thus in the symptomatology and in the anatomical picture many points of resemblance are noted.



FIG. 56.—COMMON INTESTINAL AMEBA.

If we are dealing with the former, an intestinal disease which is particularly due to the invasion of amebæ, as has lately become more and more positive, and in the case of epidemic dysentery, we are dealing with a purely bacterial infectious disease, in spite of great similarity in the clinical picture, a sharp division of both affections must be maintained. All the more so, as the clinical course, the mode of appearance and the anatomical picture of both affections, upon close observation, show many points of difference.

In the variety of dysentery which occurs endemically in warm countries there are found in fresh fecal evacuations and especially in the mucus and hemorrhagic masses of the same, small protoplasmic living organisms which show distinct alterations in shape in the presence of a certain degree of warmth sending out processes and taking up substances such as red and white corpuscles, bacteria, and the like. They belong to the protozoa and to the class of rhizopods, and these microorganisms are designated as *ameba*. Different varieties are frequently found in water, especially in stagnant water, particularly water contaminated by decomposing vegetable matter. In general, they are of no importance in man. Some are intestinal parasites, particularly of the small intestine, and are found after the administration of laxatives in the feces in normal persons (Fig. 56). Others produce stubborn intestinal catarrhs, particularly a chronic irritation of the colon. This is especially true of the *ameba coli mitis* which Quinke demonstrated in several cases of intestinal disease (Fig. 57 *a*). These cases occurred in persons that had certainly acquired the affection in Germany, but none of the severe dysenteric symptoms appeared such as arise from the presence of genuine *dysentery amebæ*, the *ameba coli* Loesch, as it is usually called. In contradistinction to other *ameba*, it is pathogenic in cats, therefore, Quinke has given it the name *ameba coli felis*. In general, it is smaller than the other species of *ameba* that are found in the intestine, but even here great variations

in size occur. Its movements are more active, its protoplasm more finely granular, and it very frequently contains red corpuscles that have been taken up, conditions which are not noted in other ameba.

Lambl was the first to find harmless ameba in the feces of children.

True pathogenic amebæ of the human colon were first found by Loesch in St. Petersburg, in the case of a farmer who suffered from severe chronic muco-purulent diarrhea; the ameba was detected in the mucus passed by the patient, and accurately described.

In the feces these ameba appear in the form of round cellular structures 25 to 30 μ in diameter, in which often a distinct hyaline, cortical substance (ectoplasm) and a granular medullary substance (entoplasm) may be differentiated. Further, they show a delicate nucleus, one or more vacuoles (Fig. 58 *b*), and frequently contain in their protoplasm red and white blood corpuscles, etc. (Fig. 58 *a*). They show movements, sending out clear, glassy, blunt processes (pseudopodia) and withdraw them again. They change their position by sending out an ectoplasmic process, the granular cell mass with the nucleus following and the end retracting.

According to Roos, these ameba become encysted, that is, they change into a permanent form, in that they take on a round to oval, sharply defined form, almost completely transparent (Fig. 58 *c*). The internal part of the cyst-form is clear, homogeneous, but rarely does a nucleus-like body appear in it; it has a diameter of from 10 to 15 μ . The ameba coli mitis, on the other hand, shows larger, quite round cyst-forms of from 16 to 17 μ , a double contour and several vesicle-like inclusions (nuclei?) (Fig. 57 *b*).

The ameba rarely show division; spore-formation has not as yet been definitely observed. Upon long standing of the dejecta the ameba decompose rapidly and, therefore, they cannot be found at the autopsy, unless the post mortem is held in the first few hours after death. On the other hand, they remain longer in the ulcers and their surroundings, especially in the submucous tissue.

Since the ameba coli was observed by Loesch, it has been found by many other investigators. Koch found them in dysentery autopsies in Egypt; he was able to demonstrate them in sections of the intestine at the base of the ulcer, further also in one of his cases, in the capillaries of the liver around a liver abscess. He was, therefore, probably the first to recognize that Egyptian dysentery is due to the ameba. Kartulis investigated this affection



FIG. 57.—AMEBA COLI MITIS. (After Roos.)

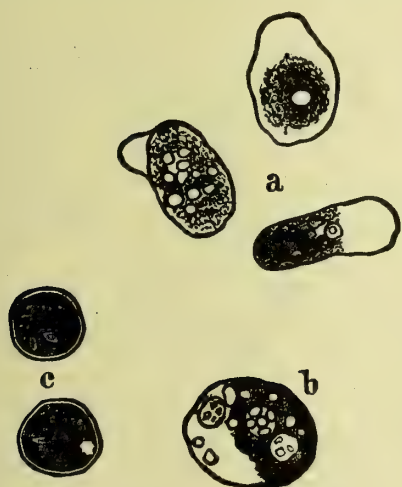


FIG. 58.—AMEBA COLI FELIS
[Loesch, dysenteriae].
(After Roos.)

further and confirmed Koch's findings in that he was able, in all typical cases, to demonstrate the ameba in the feces, whereas they were constantly missed in the dejecta of other patients. Especially did he call attention to their

connection with abscess of the liver, which is so frequent in this disease. His ameba was smaller than those described by Loesch.

Councilman and Lafleur, in a comprehensive monograph, described the anatomic and clinical conditions of the disease due to the ameba coli or as they designated it, the ameba dysenteriae, as well as its behavior in the intestinal wall, in cases occurring in North America.

Quincke and Roos studied this ameba which they recognized in cases coming apparently from Sicily and have attempted to define its relation to other harmless or less dangerous ameba, especially regarding the manner of its entrance into the intestine.

After investigations in Alexandria, Kruse and Pasquale decided in favor of the pathogenicity of these ameba. They were able to withdraw pus from a liver abscess containing ameba, but which was free from bacteria and to produce dysentery in cats; thus they obtained an important proof of the importance of the ameba in the development of Egyptian dysentery.

In numerous publications other cases were described in which ameba appeared as the generators of dysenteric affections. Many authors have busied themselves with the question of their pathogenicity, some partly favoring, some opposing this view. For the most part this concerned diseases originating from warm climates. Not rarely, however, have observations of similar cases been reported from temperate and even from cold regions.

Hlava found ameba-like structures in an epidemic of dysentery in an insane asylum in Prague. In Kieff, Massiutin demonstrated ameba in chronic dysentery.

Osler describes them in a case coming from Panama; further, Lafleur, Simon, Musser, Stengel, Dock, Eichenberg and others have reported the finding of ameba in America. Lutz declared Brazilian dysentery to be an ameba enteritis.

In similar cases in Italy, Grassi, Calandruccio, Celli and Fiocca, and others observed ameba. Their opinions, however, varied regarding the importance of these structures.

Cases occurring in Batavia and Calcutta were described by Kováčz.

Manner and Sörgo report the finding of ameba in intestinal affections in persons that have always lived in Austria.

Roemer, finally, described cases that originated in Guinea, East India, South and North America and from the region of the mouth of the Danube; he also mentions some local cases.

Cases of mild ameba enteritis, such as were accurately described by Quincke and Roos were also described by Boas.

The rich literature regarding pathogenic ameba is but briefly mentioned here; it would lead us too far to name all the observations and the various views which have been expressed in the course of years regarding intestinal ameba.

Most authors that have obtained exact clinical, anatomical or experimental opinions are in favor of the pathogenicity of the ameba coli Loesch, ameba coli felis, ameba dysenteriae, and this view is based principally upon the regular appearance of the ameba in the muco-purulent masses which are evacuated in the intestinal inflammation in question, and further, that in cats, these

ameba develop in the colon when an injection containing feces, and pus from a hepatic abscess is forced into the bowel; there develops an ulceration and necrosis of the mucous membrane with the same behavior and appearance as in human ameba enteritis. This is proved by numerous experiments which have been published at various times. A number of authors, it is true, deny the importance of ameba and refer the disease to bacteria, or they hold the pathogenicity of ameba as very questionable. This was the case with Grassi, Calandruccio, Celli and Fiocca, Casagrandi and Barbagallo, Gasser, Schuhberg, Zancarol, Sörgo, Roemer, and others.

Whereas material containing ameba, taken from a case of dysenteric ameba-enteritis, injected into the colon of cats, gives rise to the identical disease, this does not happen if it be given *per os*. According to Roos, only if the feces in question contain encysted forms may an infection of the large intestine arise, apparently, because encapsulated ameba are more resistant to the action of the gastric juice.

Pure cultures of ameba would be most suitable to determine this question of pathogenicity with certainty, but in spite of all endeavors on the part of Kartulis, Quincke and Roos, Kovács, Celli and Fiocca, Kruse and Pasquale and others, it has been impossible to obtain intestinal ameba in pure cultures. They only grow upon culture media when bacteria are simultaneously present with them. Therefore, the view has frequently been maintained that they are only capable of living with bacteria in symbiosis and that in ameba-enteritis a combined action of ameba and bacteria bring about the morbid phenomena. A condition of this kind, according to anatomic and clinical observation is quite possible. But according to histologic investigations, in autopsies from persons dying of ameba-enteritis as well as in the disease experimentally produced in cats, the ameba appear to be the microorganisms which first enter the mucous membrane and submucosa, whereas bacteria only follow them in the path which has been opened to assist in completing the work of destruction. This will be more fully described in discussing the anatomic changes and the alterations produced by experiment in the intestine of cats.

The previously mentioned experiments of Kruse and Pasquale, the transmission to the cat of ameba-containing pus from the liver which, however, is otherwise sterile, and the typical necrosis developing in the colon thereby is constituted to substitute the missing experiments with pure cultures. Naturally, the objection to this has been made that cats have a great tendency to disease of the colon, and even after slight attacks, show severe disturbances in this part of the body, therefore, the simple injection of pus will be sufficient to produce the disease, whereas the ameba need not have played a part in it. This objection, however, is of little avail because in very numerous cases injections of much more irritating masses, such as the feces from persons suffering from intestinal catarrh, but without virulent ameba, did not produce typical disease in the intestine of cats.

How the ameba reach the human intestine has not yet been determined with certainty. It is most probable that they enter the mouth by means of the drinking-water. Feeding cats with intestinal contents containing ameba frequently did not give rise to the disease, the ameba having probably been

destroyed in the stomach. However, Roos succeeded in producing infection with ameba-cysts. Calandruccio after swallowing encapsulated amebæ remained unaffected and he demonstrated them in his feces, but the question still remains whether the microorganisms were still capable of development. It is also possible that normal gastric juice destroys ameba cysts, whereas in a diminished gastric secretion, such as in catarrh of the stomach, etc., they are uninfluenced and pass into the colon in a living condition. This may also occur by partaking of improper food, by deleterious substances which are simultaneously present in the contaminated water, products of decomposition from organic material, bacteria, etc. Perhaps other permanent forms exist among the ameba, as Kruse and Pasquale, after alternate freezing and thawing of feces containing ameba, were no longer able to obtain any trace of the ameba, but by injecting them into the rectum of a cat, an enteritis with profuse ameba was developed.

Undoubtedly many observations in the tropics prove that water plays the principal rôle in the transmission of the disease. Thus, for example, it has been observed that among several ships present in the same port and whose crews had gone ashore only the crew of one ship was affected by dysentery, for this crew was permitted to bathe in the river, by means of which water always enters the mouth; the other crews that escaped the disease were prohibited from doing the same. Further, people living in districts of this kind remain free if they only take boiled water. If, however, it becomes necessary to take the water unfiltered or unboiled, or if this is done for convenience, the affection soon appears. These observations are quite numerous in the description of explorations and war-like expeditions into countries which are fertile in endemic dysentery. The report of physicians who accompanied the troops in China will probably also furnish some very interesting points in this connection. The manner in which the ameba enter the intestinal wall has been determined particularly by animal experiments; this had best be described in connection with the anatomic picture of the disease.

PATHOLOGICAL ANATOMY

At the *autopsy* of persons that have succumbed to ameba-enteritis, changes are found almost exclusively in the colon but irregularly distributed over this organ. The summit of the folds of the mucous membrane are sometimes especially implicated; for the most part the changes vary in individual parts of the colon, being distinct only in circumscribed areas, such as in the sigmoid flexure or in the ascending colon. Even in the cecum such ulcers have been found, whereas they were absent in the colon.

At the onset of the catarrhal stage the mucous membrane is partly covered by hemorrhagic mucus, it is decidedly hyperemic as is also the submucosa. The lymph follicles are often also distinctly enlarged.

Whereas this stage is but rarely observed at autopsies, the bowel post mortem frequently shows the picture of well-developed ulceration. The morbid process is particularly noted in the submucosa. This tissue is especially thickened around the ulcer, showing serous infiltration, it is soft but does not show suppuration. The ulcerations which are visible in great quantity in

the mucous membrane reach the submucosa, more rarely do they extend to the muscularis or to the serosa. The base is sometimes covered by a necrotic eschar. Provided the ulceration is not very recent, the mucosa beneath may be reached by means of a probe; often this structure is elevated above the layers beneath for some distance, so that the ulcers are connected by fistulous passages or sinuses which sometimes in the later stages of the disease produce pus. Placed in water, larger and smaller particles of mucous membrane float upon the surface of the intestine; the layers are freely movable, both forward and backward, over the deeper layers. Diphtheritic changes of the mucous membrane or superficial necrosis of the epithelium, are much rarer in ameba-enteritis than they are in epidemic dysentery. Gangrenous destruction, therefore alteration of parts of the mucous membrane into black eschars, which more or less deeply permeate the mucous membrane is also frequent. The follicles may be affected in the process, in that destruction produces small, deep, often bottle-shaped ulcers, with or without undermining the mucous membrane in their surroundings. Larger and smaller hemorrhages, ecchymoses of the mucous membrane especially in the area of the submucosa also occur. The peritoneum in the severe forms is usually markedly hyperemic; in inflammatory processes that invade deeply in connection with the ulcers slight peritonitis occurs; a soapy consistence of the serous surface of the intestine is also noted. This may increase to a fibrinous exudation so that adhesions and coalescence of the peritoneal layers occur.

I once saw a laparotomy performed in a case of ameba-enteritis in which it was possible to observe the descending colon and the sigmoid flexure. These structures were greatly thickened and could be felt even previously, by palpation through the abdominal wall as tense elastic structures resembling a thick rubber tube. The peritoneum appeared injected; numerous greatly filled blood vessels traversed the bluish-red stained intestinal wall. Upon incision, the intestine bled much more profusely than normal. The internal layers, apparently mucosa and submucosa stood out prominently. They appeared to be particularly swollen and hyperemic. After death, which soon occurred, the autopsy showed marked ulceration in the entire colon, in the surroundings of the ulceration extended separation of the mucosa from the underlying layers, briefly the entire typical picture that has just been described.

Microscopically the *special characteristic findings in the surroundings of the ulcers* are noted, namely the *collection of ameba*. They are particularly copious in the submucosa, at the border of the undermined mucous membrane, in the areas in which the submucosa is increased three to four times in thickness compared with the normal. They are found here in part in the lymph vessels, more rarely in the small veins. At the base of the ulcers they are also often found in large numbers, frequently even in the dilated lymph-spaces of the muscularis. They are rarely found in the mucous membrane and in the muscularis mucosæ, on the other hand, in these regions, great numbers of bacteria are detected. The amebæ which may thus be recognized in the tissues appear smaller than those found in the feces. They are readily detected by their round shape, their size, the generally clear protoplasm, the distinct nucleus and their behavior to aniline dyes with which they do not stain as well as the tissues of the intestine. The submucosa at the border

of the ulcer, as has already been mentioned, is markedly thickened by serous infiltration; its interstitial parts dilated, the connective tissue cells are enlarged, and partly show fatty degeneration. On the other hand, cellular infiltration of the tissue is not usually present to a decided extent. Over these areas the mucous membrane is often still intact; closer to the ulcer the submucosa reveals coagulation necrosis, destruction of the cellular elements, coagulated masses in the lymph-spaces and in the blood vessels. In the mucosa, desquamation of the epithelium, different stages of necrosis of the glandular cells and widening of the intertubular spaces are noted. At the base of the ulcer necrotic shreds of the submucosa are found. Numerous bacteria are present in the pathologically altered tissues. The amebæ are, however, always found at the most advanced areas, the bacteria are further back, in the tissue which has become more or less necrotic, having an appearance as if following the amebæ.

Diphtheritic and gangrenous parts show the usual picture of these changes in the intestine. Amebæ are usually not found in the altered tissue, on the other hand, especially on the surface, there are marked collections of various bacteria, especially streptococci and staphylococci.

Repair of the ulcers apparently occurs in this manner—the base granulates, cicatrizes, and is covered again with epithelium partly from the retained parts of the mucous membrane. Extended areas, however, show the absence of glands, and this can be noted very plainly in cases that have recovered.

The changes produced experimentally which are noted in animals, especially cats, by the introduction of dejecta containing amebæ, are in conformity with the anatomic findings in man. They show important signs in explanation of the ulcerative process and the entrance of the amebæ into the intestinal wall. Councilman and Lafleur, Kovács, Kruse and Pasquale, and Roos, have accurately studied these conditions. Especially Roos has observed the conditions of the ameba in the intestine of the cat accurately and has described them. The illustrations accompanying his article show well the manner of entrance and the disturbances produced by them. He found that the amebæ in entering the mucous membrane, here and there, give rise to necrosis of the epithelium, almost resembling the production of a toxin, which causes destruction of the cells. They then force their way further, partly in blood vessels and lymph channels between the tubules of the glands, partly in these themselves until they reach the base of the mucosa, adhering first to the muscularis mucosæ, forming large accumulations, then permeating them by way of the lymph channels, and now form large colonies in the submucosa. Surrounding them a decided inflammatory swelling develops as well as necrosis, so that thick nodules appear which then decompose, emptying themselves by a narrow passage into the intestine, and thus leaving a deep, bottle-shaped ulcer. This enlarges in all directions toward the periphery, in that it undermines the mucosa. The muscularis and serosa may also inflame and become necrotic. In how far bacteria, which enter into these defects, are implicated in the development of the changes, has not been determined. At all events, the entire picture of ameba-enteritis in the cat points to the fact that the amebæ, partly with the aid of a toxin produced by them, give rise

to characteristic alterations, and that bacteria only play a more secondary part.

The complication by *abscess of the liver* is important. This has not yet been produced experimentally but unquestionably is due to the presence of the ameba in the intestinal wall. Amebæ with and without bacteria are constantly found in the abscesses and in the walls of the abscess. As amebæ may sometimes be found in the small veins of the intestinal wall, upon microscopic investigation of sections, it is quite likely that they enter the liver tissue with the portal vein blood, and settle there. By means of this suppuration in the liver tissue great destruction may be produced. Frequently the process remains latent for a long time, as the result of formation of a strong connective tissue capsule, and for the reason that the pus possesses but slight virulent properties. Sooner or later, however, an increase in the pus formation occurs. Rupture may take place into the peritoneum, usually into an encapsulated space beneath the diaphragm, and thus a subphrenic abscess develops. Often before this, adhesions of the liver, diaphragm and lungs occur. Perforation from the pulmonary tissue into the bronchi may take place and thus evacuation of the pus and recovery occur. Further these liver abscesses may empty into the abdominal cavity or into the pleura and then produce purulent inflammation, or the pus may discharge into the intestine, rarely externally into the abdominal wall, or into the pelvis of the kidney, etc. General septico-pyemia not infrequently occurs in connection with suppuration of the liver; in the liver numerous pus foci form, as well as in other organs. In these resulting conditions, the bacteria which are simultaneously present and which may be of many varieties, play the most important part, for the pus from an abscess of the liver which only contains amebæ possesses very slight virulence.

SYMPTOMS AND COURSE

The *course* and *symptoms* in individual cases of ameba-enteritis show great variations. This is probably due to the grade of infection, the virulence of the amebæ and the pathogenic bacteria simultaneously introduced, as well as to the varying predisposition of the individual affected; particularly the locality in which the disease is acquired appears to give rise to many points of difference.

Ameba-enteritis often begins suddenly with marked watery, bilious stools; in the beginning the dejecta contain fecal masses, later more and more mucus flakes are noted in them which soon show a tinge of blood. With this there is frequent tenesmus and tormina, often also strangury. Frequently at the onset there is moderate fever, the pulse is rapid, the tongue dry, the skin loses its turgescence becoming flaccid and pale. The mucous membranes also show a decreased amount of blood. The patients are exhausted, the glance is gloomy, but the mind is entirely clear. At the onset there is sometimes nausea, vomiting of bilious masses, which however soon ceases. There is loss of appetite but usually marked thirst. Sleep is disturbed by the frequent desire to evacuate the bowel.

In other cases the disease develops more gradually, often without a rise in temperature. Accompanied with colic and tenesmus, dejecta appear which

are at first doughy, later watery and muco-purulent, and thus the same condition occurs which has just been described.

Now the disease may last for weeks and months with slight variations, showing the same symptoms. Especially at night and in the early morning there are small muco-purulent discharges with severe tormina and painful tenesmus. The patients make strong pressure, having a sensation as if the rectum were full and had to be emptied. The result is but a teaspoonful or a tablespoonful of bloody mucus. With this there may be prolapse of the red and swollen mucous membrane of the rectum which can only be replaced with great difficulty and much pain. The evacuation does not satisfy the sensation but the patient is exhausted. Soon the urgency of defecation again becomes so marked that the patients must heed it. Between these attacks, especially during the day, more fecal, doughy, and later even formed masses are emptied. The temperature is now normal or sometimes subnormal; the skin and mucous membranes, even when the amount of blood lost is not very considerable, appear pale, often sallow, as the nutrition suffers greatly and the amebæ take up erythrocytes in their protoplasmic structure and destroy them. A tendency to sweating is present. The abdomen is retracted in its lateral aspects, a stiff elastic band is felt which gives the sensation of a thick rubber tube, which is the thickened colon. Now and then colicky pains are observed localized to the region of the umbilicus. The liver is mostly enlarged, especially if a liver abscess has developed. The spleen may be enlarged, often on the contrary it is smaller than normal. In cases in which ulceration invades more deeply, and in which also very marked bloody discharges are present, peritoneal phenomena are added usually in a circumscribed area; marked sensitiveness on pressure, pain upon movement, tendency to vomiting, singultus, frequent and small pulse. Rarely does perforation with consequent peritonitis, collapse, tympany, formation of exudate, etc., arise.

In severe cases, which go hand in hand with severe diphtheritic processes or gangrene of the bowel, the disturbance of the general condition at the onset, or later after the more catarrhal, inflammatory process has passed, is very decided. The temperature especially in putrid processes is often subnormal, the pulse rapid and small; appetite is absent, marked thirst is present. The skin is covered with sticky sweat, it is pale; the lips become livid, the mucous membranes of the mouth and tongue are red, sore, fissured. The weakness increases, so that the patient no longer is able to leave the bed to discharge his feces, and then the dejecta are often evacuated in the bed without the patient paying much attention to this. The dejecta, in more diphtheritic processes, show eschars with particles of membrane in a watery, somewhat blood-tinged fluid (flesh-water). In well-developed gangrene, the discharges are brownish, black, offensive and contain shreds of necrotic mucous membrane; often also larger shreds of necrosed intestinal mucous membrane which show numerous openings at the points at which ulcers were present. The patients then in a very short time die in collapse, the mind remaining clear. In these severe forms peritonitis and perforation of the intestine occur, this hastening the lethal outcome.

Usually the sensorium is clear during the entire course of the disease, only in rare cases is there coma, a more "typhoid" condition developing.

Relapses are very frequent. Colic, diarrhea, bloody-mucus stools, etc., often return, even after apparent recovery and cessation of tenesmus and hemorrhagico-mucus dejecta. Thus, foreigners in the tropics often suffer from repeated attacks of the disease. Their only hope of recovery consists in the return to a temperate climate.

In Europe, apart from the few autochthonous cases, the disease appears particularly in a *chronic stage*. This chronic dysentery is not an infrequent affection in persons who have lived in the tropics. They are usually thin and pale, the skin often having a yellowish color. The appetite varies; it may be good, but even decided anorexia may be present. The abdomen is retracted, sensitive to pressure in its lateral aspect and in the region of the umbilicus. The colon is sensitive to pressure and can usually be felt as a thick band. Morning and night, usually, mucus or purulent dejecta are discharged with decided tormina, so that the patients are forced to rise from bed suddenly to seek the toilet. Tenesmus, as a rule, is not present, or is but slight. Sometimes the discharge is purulent, often profuse, showing a plentiful admixture of undigested food. The tongue and the mucous membrane of the mouth are usually dry, red; the gums bleed readily; there is often *fætor ex ore*. The temperature shows a tendency to assume subnormal values. Cachectic edemas appear. Later phenomena of insufficient discharge from the bowel appear, the result of cicatricial stenosis and alterations of the muscularis of the intestine. Gradually decided emaciation and consumption, weakness of the heart, bed-sores, etc., may develop, and thus after a prolonged period of invalidism the patient dies of marasmus.

The most important complication of tropical ameba-dysentery is *abscess of the liver*. Sometimes, early, but mostly only in the later course, decided enlargement and pain in the liver occur. Frequently, shoulder pain is present, almost always upon the right side. Fever of varying intensity occurs; it is often only slight, the temperature in the morning being nearly normal, in the evening rising to 100.4° F. Again, a rise in temperature to 103°–104° F. occurs, frequently accompanied by chills. Thus the temperature shows an irregular course, rising and falling, corresponding to pus fever, but it may remain at the same height for a longer time, showing but slight morning remissions. If the abscess is superficial and is situated anteriorly sometimes fluctuation may be noted; if the abscess is situated under the vault of the diaphragm, it will force the diaphragm upward and thus give rise to a dull area in the upper part of the thorax with a convex border-line extending upward. With this the intercostal spaces are obliterated or protruded; the affected area of the thorax shows great distention, not moving with respiration, but to a slight extent. Definite results are given by *exploratory puncture*; only, however, if it is positive. Often we are not successful in finding the focus, or in evacuating the pus, when the cannula enters the abscess cavity. Frequently, remissions or prolonged intermissions occur in the course of the disease. The patient imagines that he is cured, for he no longer presents symptoms or has fever; he believes that he was suffering only from tropical hepatitis. Upon investigation it is found, however, that the liver is still enlarged but no longer sensitive to pressure; and as a general enlargement, an hypertrophy, of the liver frequently occurs in people who have lived in

tropical regions, especially if they have suffered from malaria, no attention is given to this fact. But after a shorter or a longer interval, after months or even after years, during which the abscess surrounded by a capsule of thick connective tissue has remained latent, fever appears anew. The liver again develops pain, it enlarges still more; and often rupture rapidly occurs into the peritoneum below the diaphragm, a hypophrenic abscess; more rarely a fulminant diffuse peritonitis takes place, the result of rupture of the abscess into the free abdominal cavity, after a trauma or a fall. In some regions, for example in Sicily, a very common manner of the discharge of the abscess is by way of the bronchi, after a previous adhesion of the liver to diaphragm and lung, which adhesion often occurs without symptoms. The patient suddenly coughs up profuse purulent masses, which often present a red color, and for this reason do not look like pus. This expectoration may last for weeks. It may produce a purulent destruction of the lung, which may cause death; but very frequently recovery takes place on account of the slight virulent properties of the pus, the expectoration which sometimes contains bile gradually ceasing. In the sputum, in many cases amebæ have been demonstrated. Rarely does rupture occur into the intestine or into the pelvis of the kidney, the pus discharging with the feces or with the urine. Purulent exudates in the pleura and pericardium may occur through perforating liver abscesses. The discharge of the abscess through the skin of the abdominal coverings is not frequent. Perforations into adjoining organs in many cases are obviated by a timely operative opening of the abscess, and the patient recovers; otherwise, he usually succumbs, presenting the symptoms of a general septico-pyemia.

The *dejecta* in ameba-enteritis, the condition and appearance of which form the chief symptom of the disease, at the onset still contains fecal, bilious masses; but soon mucus accumulations, which have a bilious tinge, may be noted. In these latter, but not in the fecal masses, the ameba are found (Fig. 58 *a*). They may easily be recognized in the fresh dejecta which has not yet cooled. This cooling may be prevented by keeping the dejecta in an incubating oven, in warmed cloths, or the like. The amebæ are readily recognized by their active movements and their lighter color. By this condition, and also by the fact that they contain blood corpuscles, they may be differentiated readily from swollen epithelium. Also in the cooled stool, after they have become motionless, they may be noted as more markedly refracting structures, with a round shape and a distinct nucleus, often containing some vacuoles. In older cases, motile amebæ are no longer found; but only sharply defined encysted forms, such as were described in the etiology (Fig. 58 *c*), may still be noted. In the dejecta the amebæ usually disappear rapidly, for they decompose; in cover-glass preparations containing mucus particles from the stool they often remain for quite a long time. They stain poorly, and in the dejecta, by the addition of staining fluids, they are readily recognized in being conspicuous from the rest of the stained mass by their absence of color. Not rarely are infusoria found in connection with them, such as trichomonas, cercomonas, etc. (Fig. 59). The mucus which has an alkaline reaction further contains red and white blood corpuscles, ammonium-magnesium phosphate crystals, frequently also Charcot-Leyden crystals.

Though the amebæ are found readily in plentiful quantity in the mucus masses, but particularly in those containing blood, they are not so easily detected in gangrenous cases. They are probably destroyed by the enormous proliferation of bacteria.

The urine is usually diminished, concentrated, turbid, and contains indoxyl in plentiful amounts, especially if decided ulceration has occurred and in the more chronic forms. In severe cases it often contains albumin.

In how far *other tropical diseases*, such as aphthæ tropicæ, Cochin-China diarrhea, sprue and pilgrim diarrhea, are related to ameba-dysentery cannot as yet be determined. There is not sufficient knowledge in our possession at present. At any rate the clinical picture is a very similar one, and it is readily conceivable that these are but local varieties of the same disease.

A decidedly milder clinical picture, but of a conspicuously chronic character, is shown by the cases of infection of the intestine by the *amæba coli mitis* as described by Quincke and Roos. These cases are especially characterized by a tendency to diarrhea. Especially in the morning, thin mucus or pappy discharges occur. These discharges have an alkaline reaction and have a musty smell. Sometimes 8 or 9 rapidly succeeding passages occur in which, however, but small quantities are evacuated. The intestine is often flaccid and does not discharge sufficiently. If bowel washing is performed, large quantities of feces are discharged. Flatulence is frequent. In the urine plentiful amounts of indoxyl are found. The patients emaciate, partly as the result of diarrhea and the formation of abnormal products of metabolism in the bowel; partly also on account of insufficient intake of nourishment. For they fear to eat because eating brings about peristalsis or because they believe that this or that food does not agree with them. In this disease the formation of ulcers occurs in the intestine, due to amebæ; but definite autopsy findings are not at hand. Occasionally post mortem ulcers with undermined borders have been found in the colon as a secondary finding in persons that have perished from some other disease; these ulcers are believed to be due to amebæ. Upon close investigation, it may sometimes be learned that *intra vitam* there was tendency to diarrhea and also that bloody stools occurred. Often intestinal tuberculosis has been assumed in such cases. In this disease collections of amebæ are also sometimes noted in the tuberculous ulcerations. And it is questionable whether they were implicated in the development of the ulcer.

In the mild form of ameba-enteritis the amebæ are found in the discharges as described in the etiology. In the main they appear larger and less motile than the *amæba coli felis* without containing red corpuscles and are more coarsely granular (Fig. 57 a). They differ particularly from the virulent amebæ in that they are not pathogenic in cats. Frequently encysted forms are observed (Fig. 57 b), often surrounded by a mucus coat, especially in those cases in which a suitable therapy has been employed. With these, frequently, strongly refractive yeast-like bodies may be observed, as well as round, greenish, shining structures, the importance of which has not yet been determined; which probably, however, have nothing in common with amebæ,

being rather in connection with flagellæ which under these circumstances are not rarely found as parasites in the intestine.

In connection with the intestinal diseases of man produced by amebæ I desire to call attention to the occurrence and action of other protozoa in the intestine belonging to the class of *sporozoa* and *infusoria*. They often give rise to a very stubborn intestinal catarrh which in part shows a similar clinical picture to dysentery and ameba-enteritis. In their deleterious action in the bowel they are probably assisted by bacteria; but we should certainly go too far if we assumed, as was done in the case of the amebæ, to look upon them as comparatively harmless, accidental parasites, that appear in intestinal catarrh. That this is not a fact, the observation of some cases of *protozoa diarrhea* proves, for the removal of these small animals by substances which have a toxic effect on them is accompanied by the disappearance of the clinical symptoms.

Among the sporozoa there are to be considered the *coccidia* (*coccidium bigeminum* and *perforans*), among the infusoria: *cercomonas hominis*, *trichomonas intestinalis*, *megastoma entericum* (*lamblia intestinalis*), *balantidium* (*paramæcium*) *coli* besides other infusoria not definitely known and classified. The *coccidia* are rarely present in man; they occur more frequently in animals (rabbits, cattle, dogs, sheep, cats). In cattle one variety of coccidia, apparently the *coccidium oviforme*, produces a dysenteric disease, the so-called red dysentery, because the parasite permeates the epithelium, producing fibrinous inflammation and hemorrhages in the mucous membrane and giving rise to partly bloody, partly watery, diarrhea mixed with fibrinous masses. The constitutional symptoms greatly resemble human dysentery. This coccidium has also been found in man, but not in the intestine; however, it is not inconceivable that similar to the case in cattle, this parasite may collect in the human colon and there produce affections resembling dysentery. Stubborn intestinal catarrh, with marked diarrhea which decidedly influences nutrition, is caused by the *coccidium bigeminum*, which infests the epithelium of the small intestine, irritating and destroying it, and occasionally entering into the interior of the villi. The *coccidium perforans* which adheres to the villi of the mucous membrane has been found in man. The *diarrheas produced by coccidia*, on account of the seat of the parasite, are very stubborn and difficult to remove by drug treatment.

Infusoria diarrhea is more frequent in man. The diseases due to flagella: *Cercomonas hominis*, *trichomonas intestinalis*, *megastoma entericum*, and others, do not often show severe symptoms, and yield relatively easily to treatment. These parasites like the *megastoma* rest upon the epithelium, or they vegetate freely in the intestinal contents. They irritate the mucous membrane principally mechanically, thus giving rise to marked secretion and increase of peristalsis. They occur particularly in pigs, sheep, mice, rats, rabbits, and cats; and perhaps are transmitted by these animals to man by contaminated food and drink. They are but slightly resistant, and cannot withstand the gastric juice; but they form encysted varieties (Fig. 59 c) which are so much more resistant that they pass the stomach, develop in the intestine and may give rise to accumulations of infusoria. The flagella cause

diarrhea, the stools being frequent during the day, and consisting of thin watery masses with an admixture of mucus of a fecal bilious consistence, usually of a yellow color. These diarrheas disturb the patient in his subjective sensations, prevent metabolism and absorption of food in the intestine; by this means the nutrition of the patient suffers, often giving rise to weakness, especially if this infusoria diarrhea, as occurs not rarely, is super-added to other intestinal affections. Thus, we note flagella in the gastro-enteritis of children, in tuberculous intestinal disease, in carcinoma, and in ameba-enteritis, often being present in large quantities in the stool, and to their presence must be ascribed the marked diarrhea which occurs; for we note, for example, in tubercular subjects, profuse diarrhea, which affects the patients markedly, and after the removal of the infusoria this symptom disappears as if by magic.

The most dangerous infusorium is the *balantidium coli*, a parasite belonging to the cilia infusoria, or ciliates. It is found in the intestine of the pig; and thus we see that persons who have to do with these animals are particularly affected by it. It gives rise to much more severe and stubborn diarrhea than do the flagella. In the passages large quantities of mucus masses are present, blood also being often noted. According to Dehio, the balantidium gives rise to fatal dysenteric diseases which run their course with deep undermined intestinal ulcers. It probably produces a toxin which gives rise to hemorrhagic inflammation of the colon. This muco-hemorrhagic diarrhea is often accompanied by tenesmus and tormina as is the case with ameba-enteritis. It frequently accompanies amebæ and is often noted in the intestinal contents in affections produced by the amebæ. Some other, but less frequent and less virulent balantidia have also been found in the intestine of human beings suffering from intestinal catarrh.

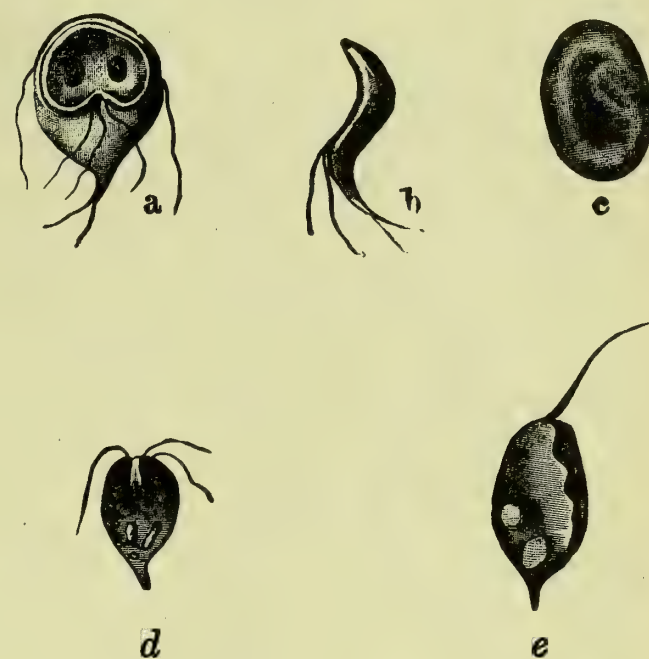


FIG. 59.—a, b, c, *Megastoma entericum*; d, *trichomonas intestinalis*; e, *cercomonas hominis*. (After Roos.)

Regarding the finding of coccidia and infusoria in the dejecta they will be noted especially, the latter better, in the mucus masses admixed with the dejecta because these are produced by the mucous membrane and for this reason contain many living parasites. The coccidia are immotile, representing oval, distinctly double contoured structures, with a net-like or granular internal structure. The infusoria, on the other hand, in freshly discharged or warm stools may be recognized easily by their active movement and the play of their flagella and cilia. The trichomonas show upon the anterior rounded portion of the body a circle of flagella, which posteriorly become

pointed (Fig. 59 *d*). The cercomonas are usually included with them, arising under the same conditions; in which, however, only one flagellum is found at the rounded end of the body as well as one undulating seam, which is

supposed to be characteristic (Fig. 59 *e*). Megastoma possess but one large sucker, with which they attach themselves to the epithelium of the intestine, several flagella being placed around it (Fig. 59 *a, b*). Further, they show two nuclei and two flagella at the pointed end of the body. Besides these infusoria there are still found oval, slightly greenish, shiny, encysted forms with a distinct capsule which appears to have a double border (Fig. 59 *c*). The balantidia are characterized by the possession of a mouth and an anal opening; they are therefore more highly organized structures (Fig. 60). They do not possess flagella, but are surrounded by cilia, which are most often in active motion.

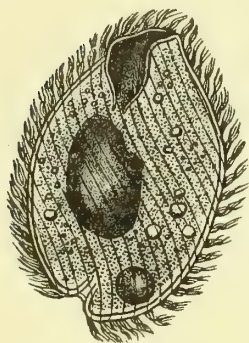


FIG. 60.—BALANTIDIUM COLI. (After Mitter.)

DIAGNOSIS

The diagnosis of ameba-enteritis is based upon the finding of the ameba; this is easiest accomplished in the freshly voided and still warm feces. Upon cooling, the amebæ become motionless and can then only be recognized with difficulty; upon longer standing of the dejecta they decompose. They keep better under the cover-glass. They are most certainly found in the mucus or bloody flocculi which accompany the dejecta, whereas in the fecal masses they can only be found with difficulty or not at all. If there is no opportunity to obtain fresh dejecta, then by means of the introduction of a rectal tube mucus may be taken from the rectum and the ameba found in it. The virulent dysentery ameba (Fig. 58) is characterized by its marked motility, by the fact that it takes up red corpuscles, and its finely granular structure, these being certain signs for differentiating it from harmless amebæ. By transmission of the feces to cats the proof of their pathogenicity is obtained with certainty. For this purpose a cat that has been etherized has some feces injected into the anus by means of a Nélaton catheter as high up as possible, and if the *amæba coli felis* be present, after a short time thin dejecta result which consist of muco-hemorrhagic masses containing large quantities of amebæ. If, however, only the *amæba coli mitis* (Fig. 57) be present which also gives rise to catarrh of the large intestine, or if other quite harmless amebæ of the small intestine be present (Fig. 56) no disease occurs in the cat after the injection.

PROGNOSIS

The prognosis primarily depends upon the appearance of diphtheritic processes. When fibrinous masses are noted in the feces, the prognosis becomes more unfavorable. This prognosis is rendered still more unfavorable when foul offensive discharges result in which gangrenous portions of the gut are found floating; therefore a gangrenous process has been superadded. Especially dangerous are those cases with subnormal temperature, cardiac asthenia and delirium. Also those cases are of questionable prognosis in which the morbid condition persists for a long time with the continuance of muco-hem-

orrhagic feces and when nutrition is markedly damaged. As liver abscesses not infrequently appear quite late after all the symptoms on the part of the bowel have disappeared we must be careful in our opinion regarding the outcome of an ameba-enteritis, especially if the disease has been acquired in warm countries. This is particularly the case if there be a tendency to fever, enlargement and painfulness of the liver.

THERAPY

Regarding *treatment*, *laxative medication* is primarily of importance. This must serve the purpose at the same time of damaging or destroying the amebæ. Most suitable for this is *calomel* in doses of from 1 to 3 grains several times daily. In those cases which persist for a longer time, that is, those that have passed into a more chronic stage, it is well to begin with small doses of about $\frac{1}{2}$ grain, two to three times daily and then in periods of about five days these doses should be gradually increased. In these patients stomatitis and gastric disturbances readily appear. After a few days, usually, good results are noted in that the dejecta become less frequent and decrease in amount, the mucus contains less blood, and the feces show more consistence. At the same time it is noted that the amebæ decrease, encysted forms or small youthful varieties appear, finally to disappear entirely.

The *root of ipecac* is especially praised. This is particularly administered in the colonies, in America, etc. Numerous quite detailed reports exist regarding its use. Usually large doses, 15 grains and more, are given, and attempts are made to avoid vomiting. A hypodermic of morphia is first injected, or opium is given. A mustard plaster or a cloth moistened with chloroform or turpentine is applied to the epigastrium. After one-half hour 15 grains of pulverized ipecac root are administered, and eventually after an hour a similar dose is given; the patient is not allowed to drink; at most small pellets of ice are given and he must remain quiet in bed. This is said to bring the process rapidly to an end. In Brazil from 30 to 90 grains of ipecac powder are administered three times in succession; from 250 to 500 cc. of hot water are poured upon it, allowed to stand, and each dose is taken at intervals of twelve hours. As a rule, this produces vomiting, but the treatment is said to be successful.

Other foreign drugs such as simaruba, pomegranate root, myrobalan, monsonia, etc., are much used. They have no advantages over calomel.

At the onset, castor oil is often given in the morning, and the treatment with ipecac begun in the evening. Magnesium sulphate and sodium sulphate have many adherents in the treatment of dysentery.

Instead of calomel, salol, 15 grains several times daily, naphthalin, in doses of 5 to 20 grains per day, naphthol, up to 30 grains per day, bismuth subnitrate and salicylate in 15 grains daily are recommended; but they are all less useful than calomel.

By *enemata*, which are applied by means of a long soft rectal tube, an attempt is made to act directly on the intestinal mucous membrane and upon the amebæ. Only the lowest portion of the intestinal tract will be reached. Disinfectants, such as carbolic acid, corrosive sublimate, etc., applied in this manner, are dangerous. Naphthalin also, on account of the difficulty with

which it dissolves, is not suitable for this purpose. One to 2 per cent. boric acid solution is better, although this may easily give rise to irritation. Quinin hydrochlorate, $7\frac{1}{2}$ to 15 grains to a litre of water, may act favorably on account of its deleterious effects on the amebæ. Astringents, as for example, silver nitrate, in solutions of $7\frac{1}{2}$ to 15 grains per thousand are not well borne. Tannin in a solution of 0.2 per cent. to 0.5 per cent. is more suitable; it seems favorably to influence the process and to shorten it. Large enemata of tannin as advised by Cantani, from 2 to $2\frac{1}{2}$ litres applied under pressure at a height of from 6 to 9 feet are said to act well in chronic ameba-enteritis; in case of deep ulceration and peritoneal irritation they are not suitable, and in acute affections it is difficult to say what changes have taken place. In acute cases they had therefore better not be employed. These drug enemata should be preceded by an enemata of Ems' water at the temperature of the body (prepared from artificial Ems' salt), to cleanse the bowel. These are also suitable for after-treatment on account of catarrh of the lower portion of the colon.

In cases which run a more chronic course there is often a tendency to constipation alternating with diarrhea. Mild laxatives are most suitable in this case; best for the purpose, if there be no great objection and a diminution of appetite does not result, is castor oil from time to time. This drug certainly acts best and its use is accompanied by the fewest disagreeable sensations. Mineral water containing Glauber's salt and laxative mineral waters are taken at home or at a Cure. They also favorably influence the catarrh and the disturbances of motility. Thus Carlsbad, Tarasp, Bertrich, Marienbad, Friedrichshaller waters, as well as the Hungarian purgative waters, also Kissingen and Homburg waters, are advised in these chronic disturbances of the colon. The vegetable laxatives, such as rhubarb, senna, aloes, etc., are also used, but are less serviceable, as they readily give rise to disagreeable irritative conditions in the intestine, spastic contraction of the intestinal musculature and therefore produce colicky pains. Combinations with belladonna preparations may lessen these difficulties. The addition of rhubarb in the use of Glauber's salt solutions, especially in gastric catarrh, is very useful. In the main, therefore, the thorough removal of feces by these remedies is much desired, and enemata must often be resorted to, or castor oil must be used. In decided atonic conditions of the intestinal wall in case deep fresh ulcers may be excluded, good results will be attained by massage, gymnastics and exercise in the open air. For the anemia and cachexia, favorable climatic conditions are advisable; the climate should not be cool and there should be little moisture and but little wind, therefore not too high mountainous regions. The use of iron and arsenic preparations is to be advised.

The affections which are to be referred to the *amœba coli mitis* often react promptly to calomel treatment in the manner previously described and to enemata of quinin and tannin, in that the feces become more compact, diarrhea ceases, and nutrition improves. But it is difficult to remove these parasites entirely from the intestine; for this reason relapses frequently occur. The favorable influence of an evacuating, and often of a disinfecting treatment, consists partly in damaging the intestinal bacteria, which in connection with the ameba bring about changes in the mucous membrane.

Among the *infusoria* the balantidia are very resistant to therapeutic measures, perhaps because, in contradistinction to the flagella, they occupy a more protected position, deep in the ulcers of the bowel. Quinin in them is an active poison; therefore, after the employment of enemata of quinin, $7\frac{1}{2}$ to 15 grains to the litre, and the administration of cinchona root, 15 grains three times daily, best given in capsules, favorable results are obtained. Dehio has seen good results from the use of filix mas whereas other observers saw no action from this remedy. The most certain method of treatment consists in the use of calomel, which is administered twice daily for a period of five days $\frac{1}{10}$ grain each dose, increased to 3 grains after a use of from two to three days. This treatment with calomel in intestinal catarrh due to flagella (*trichomonas*, megastoma, etc.) accomplishes rapid improvement of the diarrhea and the removal of the parasites from the dejecta.

Coccidia resist this method of treatment tenaciously, probably on account of their deeper seat in the epithelium and the villi of the intestine; but the catarrhal condition produced by them is improved by the use of this remedy.

In regard to *diet*, I may be brief. In acute ameba-enteritis the same diet is to be used as in the onset of epidemic dysentery. But small quantities of luke-warm tea, flour soups, diluted milk and milk soups are permitted; later, undiluted milk may be given with advantage. Some patients, however, do not digest milk well, suffering from marked fermentation in the stomach and intestine, constipation and colicky pains. As the disease is prolonged and the patients in consequence become anemic and cachectic, a one-sided diet must not be too strictly adhered to, and for this reason tender lean meat, easily digested starchy foods and vegetables, wheat bread, rolls, zwieback, eggs, some butter, etc., may be ordered and an alkaline, saline mineral water, should be used in connection therewith. Wine may be given in moderate amounts without damage; beer must be given with caution, best in the form of pasteurized export beers.

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CHOLERA NOSTRAS AND CHOLERA INDICA

By TH. RUMPF, HAMBURG

ETIOLOGY

S., a workman, aged thirty-seven years, was admitted to the hospital eight days ago suffering from *diarrhea*, followed by lassitude and inability to work. The number of movements was said to be from 13 to 14 per day. After this apparently causeless diarrhea had lasted for six days, a decided aggravation in the condition occurred. The diarrhea became more pronounced, *vomiting* without decided *abdominal pain* arose; to this high-graded *asthenia*, *cramps* in the *calves*, and *hoarseness* were added and as this condition persisted the patient was sent to the hospital.

The appearance presented by the patient was that of a thin but powerfully built man; his eyes were deeply sunken in the orbits; the skin was dry and cool, the color livid and the wrinkled skin could be raised in folds without difficulty. The abdomen was retracted, slightly painful upon pressure. There was *hoarseness*, the nose and extremities were cool and moist; the pulse was almost imperceptible; the profuse stools had the appearance of *rice water*. The lungs showed no deviation from the normal, the heart sounds were extraordinarily soft; liver and spleen were not enlarged. The temperature was 97.2° F.; the urine discharged in very small amounts contained albumin.

It was a severe clinical picture which the patient presented upon his admission. The small pulse, the feeble cardiac activity, prompted my assistant, Dr. Reiche, to at once give the patient a *subcutaneous infusion* of 1,000 cc. normal salt solution, of a temperature of 104° F. (in the irrigator) and a short time after the absorption of this amount of fluid the condition of the patient improved. The *hoarseness disappeared*, the *pulse* became *slower* and *fuller*; the extremities became warm. Hot tea was then administered to the patient and he passed the night in a comparatively comfortable condition.

The following day the condition of the patient was not so good, the rice-water stools were still present, the extremities were cool and the abdomen was somewhat tympanitic.

The patient was then given a hot bath at 32° R. lasting a quarter of an hour and on account of the presence of masses in the intestinal canal which caused tympany one-half a gram (7½ grains) of calomel twice in the course of a day was ordered. After the hot bath the patient was placed in *woolen blankets*, *hot drinks* as well as *gelatinous soups* being administered in plentiful amounts.

Thence on a decided improvement was noticeable. In twenty-four hours only five thin stools occurred, of which the last showed a yellowish discoloration; the pulse is better, the cardiac action more powerful, the scant excretion of urine, in twenty-four hours, has risen to about 1,200 cc. with but a trace of albumin being present. The color of the patient is normal, the nose and extremities are warm, briefly, the patient is in the stage of convalescence. Naturally, the patient must be kept in bed, and should his condition again become aggravated the previous therapy will be again employed; I believe, however, that as the result of the favorable influence of the treatment this will no longer be necessary.

In examining this clinical picture we must designate the condition as a severe *gastro-enteritis*; but it was characterized by another symptom, by *simultaneous toxic phenomena*.

Since ancient times this form of disease has been designated by the name of *cholera*, and it is our object to examine into the cause of the clinical picture in a concrete case. Two extraordinarily different etiologic affections, which in their clinical picture show many like conditions, bear this name. While the one form occasionally appears sporadically, at times in small epidemics, the causes of which may be extraordinarily varied, the other represents an affection, the great importance of which depends upon its pathogenic agent, which has its constant home in India and from there may be transmitted to the most distant countries, causing decimating epidemics. This pathogenic agent has been regularly found by Robert Koch in the dejecta of *cholera patients* who have come from India. In the case just detailed we must, therefore, carefully examine the *dejecta* to search for the cause of the disease.

From the *rice-water stools* we took small mucus flocculi and examined them under the microscope. We saw, besides granular masses of detritus and some few epithelial cells, a large number of microorganisms of various forms and size, large and small rods and also micrococci. Some of these microorganisms were quite motionless in the field of vision, others appeared to have distinct movement. But among these various forms of microorganisms we saw no variety which was more numerous than the other. *This preparation did not permit of an opinion regarding the etiology of the disease.* We then took another plug of mucus, smeared it in a uniform direction upon a cover-glass. After the preparation had become dry in the air it was drawn through a gas flame and stained with gentian violet. We now saw a picture resembling the first preparation, but the various microorganisms being stained, were more distinct and immotile. Even this preparation did not allow of definite conclusions. In dealing with a severe and typical case of Indian cholera we would have noted the pathogenic agent, the rods denoted *comma bacilli* by Koch in a uniform arrangement, like fishes in a flowing brook. But the probability that cholera vibrios, besides other microorganisms, were present in the dejecta had to remain undecided, and soon after the admission of the patient the question was more minutely investigated whether cholera vibrios could not be recognized in the dejecta in other ways.

First we prepared a peptone culture according to Koch's process. A sterilized watery 1 per cent. peptone solution and 1 per cent. sodium chlorid solution which was rendered strongly alkaline and in which one or more platinum loops of the stool were contained were put in the incubation oven at a temperature of 37° C. Cholera bacteria, as Schottelius was the first to show, as the result of great necessity for oxygen, endeavor to reach the surface of the culture media and there increase to a decided amount. Six to twelve hours after preparation of the culture, a *pure culture of comma bacilli* is often found upon the surface of the peptone solution. A culture from this case only revealed some isolated rods which showed no resemblance to cholera vibrios.

We then prepared a gelatin plate culture, a flake of mucus being divided in a 10 per cent. nutrient gelatin, two dilutions being made and poured upon three plates which were placed in the incubation oven at 22° C. The first plate contained the entire mucus flake, the second and third each 1 drop from the first plate and the third plate 1 drop from the second. If cholera vibrios were contained in the dejecta in forty-eight hours at the latest we should note

round colonies, of a typical appearance, with slightly irregular borders on the plates, and the microscopic preparations of these plates would have to show a pure culture.

In examining these plates, upon the third some few colonies are noted which in *contrast to cholera vibrios* show round umbilications rendering the material upon the plate fluid. Similar pictures, with confluent colonies were shown upon the first and second plate. These colonies can certainly not be looked upon as cholera colonies and even in the microscopic preparation the rods of these colonies show no resemblance to cholera vibrios.

We, therefore, arrived at the result that our patient did not suffer from *Indian cholera* but from an *endemic form* (**cholera nostras**), which perhaps had better be designated as *cholera morbus* (Brechdurchfall).

This affection shows special preference for the hot seasons, particularly late summer, so that American authors have designated it by the name "*summer complaint*." However, in autumn and in winter cases occur due as a rule to food in which decomposition or admixtures of a deleterious nature are present. If in any large number of persons the same deleterious substances are introduced into the intestinal canal, group diseases arise of greater or lesser extent.

Naturally, decomposition of food occurs more frequently in the hot season than in winter. The cause of this depends particularly on the fact that these decompositions occur from the action of schizomycetes which require a certain amount of heat to develop profusely. That, however, also without schizomycetes, poisonous substances may be present in the food and give rise to the picture of cholera nostras, is shown by *similar affections* which can only be produced by *poisons* like solanin and colchicin. Some *foods* may also contain toxic substances without the action of schizomycetes. In the case of *cheese* this appears to be questionable to me, on the other hand, *cow's milk*, under some circumstances may contain toxic substances (Alt).

Fish poisoning also appears to arise without the action of bacteria, at least typical toxic symptoms are not rare after partaking of quite fresh fish of a certain kind.

These *intoxications* may be analogous to those cases of poisoning from *mytilus*, accurately described by Schmidtman, in which the poison is also pre-formed and above all is contained in the liver. It is true the clinical pictures produced by this form of intoxication more closely resemble paralysis than cholera, and the great majority of cases of cholera nostras after partaking of fish are rather due to stale and decomposed fish by the action of schizomycetes or fish which still contain schizomycetes. In this respect a communication by Ziber is of interest, who believes the *bacillus piscicidus agilis* responsible for a form of fish poisoning; he was even able to demonstrate the bacillus in the stools of two fatal cases which resembled cholera. Also the cases of cholera nostras arising, now and then, after *partaking of oysters* may be explained in a similar manner.

The same, in general, is true of *meat poisoning*. Here also an analogy with *belladonna poisoning* may be considered in that the animals during life accumulate toxic substances in their bodies without damage to them, which, after they are killed, produce pathological conditions when their meat is eaten.

Most frequently the cause of these affections, however, depends upon schizomycetes which form toxic substances upon the food or in the intestine, thereby producing the clinical picture of cholera nostras.

Bacteriology has devoted itself to the discovery of these microorganisms with great energy. Finkler and Prior in a small epidemic of cholera nostras in Bonn in 1884, found a vibrio in the dejecta resembling cholera, which they looked upon as the cause of endemic cholera morbus. A similar vibrio was only discovered once more by Host. A bacillus, which rapidly liquefied gelatin, producing a marked stench, was isolated by Mayhöffer, while Hüppe noted in the rice-water stools of endemic cholera morbus short bacilli which did not liquefy gelatin, which he regarded as belonging to the typhoid group.

Fischel and Enoch cultivated rod-shaped bacteria from a carp that had developed ecchymoses. The meat of the carp, cooked and fed to dogs, produced vomiting and diarrhea.

Gärtner found in the meat of a slaughtered cow, of which 58 persons had eaten and were made ill, a special bacillus, not liquefying gelatin, which he designated *bacillus enteritidis*. The same bacillus was found as the cause of cholera nostras in 27 persons, in the province of Posen by Günther. Gaffky and Paak isolated a motile bacillus from *sausage* which they regarded as the cause of cholera nostras; in apes it produced diarrhea and death. Karlinski, van Ermengen and Lubarsch made similar discoveries. Kaensche, Pottien, Klein and my assistant Dr. Fricke found various forms of bacteria, partly with and partly without the power of movement, some having the property of forming capsules. Feeding animals with pure cultures of these caused symptoms closely resembling cholera.

By most authors the bacterium coli was found either in pure culture or mixed with other forms. Bleisch and B. Fischer found cholera-like vibrios as the cause of cholera morbus; Dunbar and Vogler found peculiar bacilli, also resembling those of cholera, in the Elbe and other rivers, upon the shores of which cases of cholera had occurred. As these bacilli also produced diarrheic diseases, and on account of the methods then known, could not be differentiated from the vibrios of Indian cholera it was obvious that these were true cholera bacilli. Succeeding Kutscher and almost simultaneously with him, Oergel and Willgerodt found that a part of the vibrios obtained by Dunbar from rivers showed a property which was only present from time to time. We will return to the importance of these vibrios, especially their differentiation from cholera vibrios, later on.

Lately the occurrence of *spirochetæ in cholera nostras* has been noted by several observers; they are also occasionally noted in Indian cholera. In both diseases they are probably more of a secondary finding. In 1892 in Hamburg, they were observed in several cases of cholera indica.

The observations just mentioned, however, are not the regular ones. Compared to the profuse amount of microorganisms in fresh dejecta, a gelatin plate culture, a 1 per cent. peptone-salt solution and a second gelatin plate culture taken from this, as a rule, give but very few forms. For the most part they are but varieties of proteus and bacterium coli.

The results of these investigations show *that a uniform etiology for cholera nostras does not exist*, that, moreover the most varied toxic substances, which

are for the most part produced by microorganisms are capable of producing cholera nostras. A special predisposition of the organism may also be necessary, as was shown by Fricke's investigations, who was only able to produce the severe clinical picture in dogs from the first feeding.

There is rarely an opportunity for *pathologico-anatomic studies* of cholera nostras. In those cases in which a necropsy has been held the mucous membrane of the intestine is mostly reddened and denuded of epithelium; hemorrhages and eschars have also been observed in the intestine. In an especially severe case of cholera nostras in an adult, who died in coma, Jollasse believes that he also observed severe pathologico-anatomic changes of the *renal epithelium*.

DIFFERENTIAL DIAGNOSIS

The *differential diagnosis* between cholera nostras and Indian cholera is frequently difficult. There is, however, great necessity for this, especially where there is danger of importation of Indian cholera. As since 1893 no cases of Indian cholera have occurred in Hamburg and the last epidemic may be looked upon as finished, the probability in the patient whose history was previously cited was great that we were dealing with an endemic form of the disease. Nevertheless, it must always be remembered that with modern facilities of travel, the possibility of importing the disease from other countries is very great and that in every case that resembles cholera it is our duty to search whether there is any probability of the case coming from a cholera focus. We must, therefore, do everything to determine the diagnosis bacteriologically. In a large hospital, with which a bacteriologic laboratory is connected there are no great difficulties; in private practice it is not always possible for the physician to resort to a bacteriologic diagnosis. But in this respect many institutions and universities are able to carry on these researches. In sealed glasses, well packed, small quantities of a fecal discharge may easily be sent for investigation, in which case, however, it is always necessary that care is exercised so that no transmission of the disease occurs, by means of these dejecta. It is true, the method of infection, in all cases, cannot be followed absolutely and this circumstance has led to the fact that the etiology of cholera, for so long a time, gave rise to a diversity of views.

HISTORY OF CHOLERA INDICA

There can be no doubt that Asia is the home of cholera indica (cholera Asiatica).

The home of cholera is in the southern part of the province of Bengal, in the valleys traversed by the Ganges. The capital of this region is Calcutta. In this area cholera exists, to a moderate degree, year in and year out, frequently in the manner that its maximum occurs in April, a month characterized by great heat and rain, its minimum occurring in the hot and wet month of August; this relation, however, cannot be regarded as a hard and fast rule.

According to the descriptions of Bryden this region shows a climate of constant heat and humidity, due to its low position, in comparison with the

surrounding mountains, as well as to the enormous masses of water which the Ganges and Brahmaputra send through these areas in their many branches. The moisture of the earth is further increased by a frequent southeast wind, which often brings rain during the period designated as hot and dry.

From the *endemic area* just described cholera distributes itself year in and year out over smaller and larger portions of India and in neighboring areas in Asia, and from this region, in six epidemics, has attacked Africa, Europe and America. The minute investigations of Macpherson point to the fact that the first Europeans who came to India, the Portuguese, already found cholera as an endemic, occasionally epidemic disease. As early as the year 1543, a great cholera epidemic was said to have been observed in Goa. Macnamara even places the age of cholera further back, according to this author, cholera was known long before the Christian era. The Indian Esculapian, Tscharaka, who, according to the belief of the Hindoos, was immediately instructed by the God Dhanwantari and whose pupil Suçruta, who lived ages before Christ in the Northwestern provinces and displayed his activity there, had unquestionably described cholera, from the beginning of the disease with diarrhea and vomiting up to the blueness of the lips and nails in the cold stage of the disease to the *vox cholericæ*. The disease was designated as *wischutschika* or *wischutschî* (vomiting-dysentery), also *nirtiripa* (intestinal colic, Bartolomeo) and by some authors as *mordechîm* (rapid death?).

Doubts regarding the antiquity of cholera have arisen, particularly on the part of R. Koch. He believes the reports, regarding older epidemics, as uncertain and expresses the view that prior to 1817 true cholera was not endemic in any part of India. For this reason and on account of the successful prophylaxis in Madras, Calcutta and Bombay, Koch hopes that it will be possible to confine cholera to India and then to cause its final disappearance.

This criticism of Koch's has caused me to request my former colleague in Marburg, Prof. Justi, to search ancient Indian literature, regarding this point. According to Justi's view, Suçruta, who founded the system of Indian medicine lived between the sixth and eighth centuries, A. D.

The description of *wischutschika* by Suçruta, the translation of which I owe to Prof. Justi, very closely resembles the picture of Indian cholera. After describing various disturbances, such as diarrhea, vomiting, thirst, stabbing pain, loss of consciousness, he says further: "Man whose teeth, lips and nails are blue, whose consciousness is feeble, who is tortured by vomiting, whose eyes have sunken in, whose voice is weak, whose joints are all loosened, may return to the text-books." As, however, in India sporadic cases of non-epidemic cholera occur, the absence of distinct reports regarding the epidemic character of the malady, renders a definite opinion impossible. But another source points to this. In the Veda, which is in part older and in some portions of the same age as Suçruta's work, a verse occurs in which the *wischutschika* is personified and worshiped as the Pest Virgin. "The *wischutschika* which spares both tiger and wolf and does not attack the feathered hawk nor the lion may save these from anguish and distress." That this is a prayer to ward off the pestilence is even plain to us; that such a prayer does not owe its origin to sporadic cases of cholera morbus appears to me and also to Prof.

Justi as improbable in the highest degree. Nevertheless, I should not like to fail in adding that Albrecht Weber, the prominent Sanscrit investigator, has expressed himself in a different manner in regard to this verse.

We possess a more forcible proof of the existence of cholera before 1817 in Sonnerat's description of his travels in East India and China. Sonnerat reports, that in a few years 60,000 human beings died of a pestilence, the symptoms from which they suffered consisting of watery diarrhea (often 30 in five to six hours) with vomiting, total loss of strength, burning thirst, anxiety, anuria, loss of speech, coldness of the hands and ears, and sinking of the orbits. I do not know what other epidemic disease but cholera could be meant by this description. After this great epidemic a period of rest appears to have occurred.

The next reports of this pestilence date from the year 1817. After the affection had already appeared in Bengal in 1816 it appeared in August, 1817, in Jessur and spread, producing a high degree of mortality and causing great panic, from district to district, over the greatest part of the Indian peninsula. Combined with this appearance of cholera in 1816 and 1817, the first pandemic occurred, which spread over a large part of Asia, the east coast of Africa and a small portion of Southern Russia. In the second pandemic, which began in the year 1826, a larger portion of Russia, the provinces of Posen, Silesia, Pomerania, Brandenburg, Hamburg, Austria, England, France, the Netherlands, Norway and Sweden, Canada and the United States, Portugal, South America and Italy were affected. The pestilence only disappeared in the year 1838.

In the third pandemic of 1841-42, Arabia, Turkey, Russia, Poland, England, Holland, Belgium and France were severely attacked. Emigrants brought the disease to the United States, Central America, Denmark, Sweden, England, larger areas of Germany and of Switzerland were attacked by the disease; Brazil, and thence, later, South America was implicated. This pandemic only ceased in the year 1860. As early as the year 1863, the fourth pandemic began, which primarily attacked Asia, then Russia and Germany were severely affected. The malady also appeared in the United States and in 1875 the fourth pandemic appeared to have terminated.

In the year 1884 cholera reappeared in Egypt, in the countries bounded by the Mediterranean, especially Italy (Naples), in Spain, Austria, South America, Japan and Dutch India. A quite isolated epidemic, the origin of which has not yet been cleared up, in which 14 fatal cases occurred, broke out in Gonsenheim and Finthen, near Mayence. Then followed a few years of rest until the year 1892 when the pestilence traveled over Persia, Russia and in an unknown manner reached Havre and France. Quite a sudden epidemic occurred in the middle of August in Hamburg, in which within two months 9,000 persons perished. In connection with the Hamburg epidemic, isolated foci of the disease were noted in Germany, thus, in the Institute for the Insane, Nietleben. But in the following years cholera also occurred in Russia, Spain and in isolated districts of Germany.

ETIOLOGY AND SYMPTOMATOLOGY OF CHOLERA INDICA

Cholera has been a favored field of investigation by physicians for a long time. This interest has not been without reward, for we may state, with a certain degree of satisfaction, that the research in the investigation of cholera has given us important biologic and clinical insights into the nature of infectious diseases in general.

One of the most important clinical experiences is this, *that the introduction of the infectious agent into the human body by no means always results in disease*. For the production of the disease a constant or only momentary *predisposition* is required. As has already been stated, in cholera indica, Koch's cholera vibrios are constantly found; it has occurred, however, that in cases in which the stool was even solid cholera vibrios were demonstrated. In some of these cases diarrhea had preceded, but in individual cases also this symptom was absent. Such cases were brought to the hospital because the disease occurred simultaneously in the family or in relatives, so that a possible infection was thought of. Many cases refused to remain in the hospital and they regarded themselves as quite well, and it required great power of persuasion to retain them until the cholera vibrios could no longer be detected in their dejecta. Similar experiences have also been gained in other infectious diseases.

If infection occurs in a person who is predisposed, clinical symptoms arise which vary from the mild cholera diarrhea and cholerine up to the condition characterized as *cholera gravissima*.

Cholera diarrhea includes about one-third of all cases and shows as a characteristic symptom the presence of cholera vibrios in the dejecta; these organisms have been cultivated up to the forty-eighth day from the apparently normal stool. In feces that have been saved for three months, animate vibrios have been found. Now and then cholera diarrhea passes into *cholerine* and *cholera gravis*.

Much more frequently than from a diarrhea which has existed for some time does

CHOLERINE

develop as a form, *sui generis*. Frequently this affection is ushered in by disturbances of a general kind. *Lassitude, sensations of fatigue, anorexia*, often also *nausea* is present, then suddenly, frequent diarrheic stools follow, which at first are yellow but soon become rice-water like. Without the stools becoming especially frequent *vomiting* now occurs. This first consists of food which is vomited; then the vomited material becomes greenish-yellow, it is very fluid and accompanied by an exceedingly bitter taste. Rarely is the vomited material completely discolored, resembling whey, or rice-water like. After repeated attacks, the vomiting may cease while the diarrhea continues. Loss of appetite, coated tongue, pains in the epigastrium, high-graded weakness, tinnitus aurium, vertigo, headache and marked thirst appear, with an aggravation of the pathologic picture. Now and then, a rise in temperature occurs which, however, cannot be noted without the use of

the thermometer. The skin as a rule is cool, the pulse is usually small; the excretion of urine is slight or absent entirely; *in the scant urine albumin is found*; frequently drawing pains in the calves are complained of, without cramp being necessarily present. If the affection develops further we see the typical picture of cholera. Frequently, the patient recovers from this described picture of cholera, but this is not always rapid. In the first place, diarrhea from the slightest cause returns anew, frequently, later on, a *febrile or afebrile* condition occurs with general weakness, slight sweating, coated tongue and marked thirst.

As well as the condition of cholera may ameliorate, on the other hand the severe picture of

CHOLERA GRAVIS

may develop. This can best be illustrated by the following clinical history of a young merchant, aged thirty, admitted to the hospital in September, 1893. This patient had but little diarrhea and then vomiting, lassitude, tinnitus aurium and palpitation occurred, with a sensation of pressure in the cardiac and gastric regions, accompanied with great anxiety. Presenting the picture of a severe affection, with *cyanosis* of the skin, *sunken eyes*, he was admitted to the hospital. From time to time, vomiting occurred, while diarrhea was absent. An indescribable fear distorted his features, the *muscles of the calves were spasmodically contracted*, and occasionally the spasm also appeared in the biceps; cold perspiration covered the forehead, the *bluish-gray skin* could readily be raised in folds. The *nose and extremities* were *cool* and blue; while the patient constantly threw himself about, in a hoarse voice he declared that he did not wish to die, he asked for fluid and vomited what he had taken. A hot bath, a normal salt infusion only transitorily improved the condition; his temperature fell and after a few hours the patient succumbed to his agonizing affliction; even in death his arms and legs were spasmodically contracted as if entering the arena for the combat.

Not in all cases does death occur preceded by such torments. Some patients are apathetic and somnolent, but when they are aroused it may readily be noted that the psychic functions are quite normal.

In the severe stage the temperature usually falls. This drop, however, is rarely as great as it may seem. Temperatures below 95° F. are not frequent, but on account of the simultaneous moisture of the skin, the loss of heat appears to be much greater. The pulse for the most part is weak as a rule, but of normal frequency; it is rarely accelerated and then not above 100 per minute. Frequently, from hour to hour, the pulse becomes less perceptible; in the carotid and crural arteries it becomes indistinct; the second sound of the heart disappears; small arteries and veins when incised, scarcely bleed. The respiration, as a rule, is accelerated. Even without organic disease of the respiratory organs, there may be from 30 to 40 respirations per minute. The secretion of urine has either ceased entirely or the amount is greatly diminished, but there are also cases in which a plentiful excretion of urine is observed. Thus, I have seen a patient, thirty-nine years of age, who in the algid stage of the disease in twenty-four hours, and also in the succeeding stages, voided 1,250 cc. of urine. This urine contained 10 grams

of N. and 2.075 grams of ammonia. The abdomen for the most part is retracted; upon percussion, as a rule, a slightly dull note may be obtained and if the cutaneous coverings are not too thick, the splashing of fluid may be noted, which fills the intestines, even in the absence of diarrhea.

This hopeless condition frequently terminates in *death*, in other cases a *surprising recovery* may result without definite reasons being apparent in the clinical condition for this change in the outcome of the disease. While the vomiting desists, the profuse diarrhea ceases, the pulse improves, the color of the patient becomes better and in the course of a few hours recovery, from the severe attack, has taken place.

But the *severe, algid stage* is also subject to great variations, as the result of treatment.

After the use of *hot baths* and above all, as the result of subcutaneous and *intravenous injections of normal salt solution* an almost magical effect is produced in some cases; the pulse improves, the cyanosis and the gray discoloration of the skin disappear, the eyes which are deeply sunken in the orbits show life, the respiration becomes deeper and regular, the spasms cease, the face has some color, the temperature becomes normal and a beneficial perspiration appears. Patients who were previously apathetic, somnolent, not reacting to stimulus, who paid no attention to the injury of the skin produced by exposing the vein to permit the influx of the salt solution, often awake as from a deep sleep, and the rough, hoarse cholera voice becomes clear and intelligible. As if by magic, the desperately ill patient has been transformed into an apparent convalescent. *This brilliant result is, however, not always permanent*; in spite of the continuance of the treatment, the algid stage reappears after a few hours and although the infusions are continued does not disappear permanently. In a somewhat protracted course of cholera many patients succumb. Other cases appear to enter into the stage of convalescence, but this change is not permanent. The algid stage has disappeared, the pulse has again become full, the respiration regular, the face shows some color, the voice has lost its hoarse quality—but the entire condition which the patient presents is still peculiar. A state has developed, which the older authors have included under the name of *cholera typhoid* and which, to avoid confusion, I should like to designate as *coma after cholera*, or as

STADIUM COMATOSUM OF CHOLERA (CHOLERA TYPHOID)

The patient who perhaps for a few days has appeared to be on the road to recovery, suddenly falls into a condition of *great weakness and apathy*. Now and then, he complains of *vertigo and of headache*; the latter symptom may often only be surmised from the fact that the patient is in a condition of *stupor* and from time to time grasps his head with his hands.

In other cases this condition, just described, is connected at once with the algid stage from which the patient has just recovered; this has been particularly noted after the use of salt infusions. If the *temperature*, after passing through the severe attack, has returned to normal or for a short time has even gone above this range, in the severe cases now a drop occurs; the tendency of the extremities to become cool, which was previously present, reap-

pears; cyanosis again becomes noticeable, while the pulse may frequently be full and strong.

In contrast to the *cool extremities*, the head is often hot, face and conjunctiva are injected, speech is indistinct; hearing is impaired and either delirium appears, which in some rare cases leads to prolonged stages of excitement, or the patient becomes apathetic and somnolent. With this, spasms in the muscles continue or begin anew, diarrhea is common but does not reach the previous intensity. The discharges are characterized by the fact that cholera vibrios are always demonstrable in the dejecta, while in the secondary diarrheas, as a rule, no cholera bacilli can be found. The presence of these bacteria, during so long a period, is the reason why I should like to refer this clinical picture, which was formerly looked upon as a secondary affection, entirely or for the greatest part, to intoxication, and this is also the reason why I have designated it as a chronic cholera intoxication. The secretion of urine is frequently reduced or anuria is present, voluntary evacuation of the bladder is rare. *Stupor and coma* gradually develop from the *somnolence* and thus the patient perishes. In other cases, a condition resembling the algid stage arises, which terminates in death from exhaustion. Although the condition appears to be extremely severe some cases may recover. As a rule, improvement occurs with the eruption of a *peculiar exanthem*. This is sometimes in the form of an *erythema*, or it may resemble urticaria or large roseolar flakes; these eruptions may spread over the arms, chest, back and often even over the entire body. From *coalescence* of the individual parts of the eruption, a general cutaneous redness takes place, which only in isolated areas, in which it has developed, shows that it consists of individual flakes. This exanthem may remain pronounced from one to three days but, as a rule, it soon fades after its appearance. Somnolence and apathy may vanish with the appearance of the exanthem, the symptoms on the part of the gastrointestinal tract may ameliorate and gradually convalescence may set in. Frequently, however, this convalescence is deceptive. Vertigo and somnolence reappear, the diarrhea becomes more copious and the stools may even contain blood, the pulse becomes rapid and thready, the respiration stertorous, and without any additional symptoms, death occurs.

The prognosis is particularly *unfavorable* in those cases in which a *sub-normal temperature* introduces the picture of the severe intoxication.

In 183 carefully investigated cases of this variety 165 perished, giving a *mortality of 90 per cent.* The cases in which less severe symptoms on the part of the nervous system, and those in which fever occurs, are of more favorable prognosis. Naturally I do not include those cases in which complications are the cause of the fever. The fever may be the only symptom, but it is usually accompanied by a certain degree of apathy and somnolence. With the eruption of the cholera-exanthem, convalescence may set in suddenly, headache, apathy, somnolence disappear, the mind becomes clear, the tongue clean, the appetite returns and comparatively rapid recovery results. These forms of chronic intoxication may occur in isolated cases, in cholerine or also in connection with a prolonged cholera-diarrhea.

Among the symptoms which accompany this intoxication, one of the most frequent, is a decrease in the *excretion of urine*. However, I have also seen

coma when the excretion of urine has been plentiful. *Albuminuria*, which is present in most cases, may also be absent or may be very slight. Griesinger, on account of the frequent appearance of the last mentioned symptoms, was inclined to attribute a part of these cases, which he had termed *typhoid*, to uremia. However, I should like to attribute all these symptoms to toxic substances, which originate partly from cholera-vibrios and partly from a severe disturbance of metabolism. I have lately observed a similar clinical condition with the same exanthem in a case of corrosive sublimate poisoning.

It may be conceived that *toxic substances* play a part in the comatose stage of cholera, on account of the demonstration of profuse amounts of cholera vibrios, for a long time, in the dejecta of these patients, and then also because of the pathologico-anatomic condition of the wall of the intestine. The surface epithelium of the intestine, in many autopsies, is found desquamated; but it is of especial interest that great numbers of cholera vibrios are found in the inner portions of the intestinal wall, some in the *villi*, which may be *necrotic*, and others in the lumen of Lieberkühn's glands; that the epithelium of the convoluted uriniferous tubules shows the same severe changes that we are accustomed to note in many other intoxications and in some of the infectious diseases, and that these last named changes are also observed in cases in which a decrease of fluid in the blood can be excluded. The experiments of R. Pfeiffer are demonstrative in the same sense; he was able to produce a toxic affection in guinea-pigs, by the intraperitoneal injection of a minimum quantity of an eighteen hour old culture of cholera vibrios; the result was a fall in temperature and fibrillary contractions, followed by death of the animal.

SERUM DIAGNOSIS OF CHOLERA

We must now devote our attention to the interesting phenomena regarding cholera which we have learned to recognize through the investigations of R. Pfeiffer; these have also become of importance in many other infectious diseases. Pfeiffer, in his experiments, attempted to determine an easy method of differentiating true cholera vibrios from similar forms. Varieties of this kind were frequently demonstrated during the last decade and they often gave rise to confusion with cholera vibrios, for in the animal experiment they were also capable of bringing about a lethal termination. A part of these comma bacilli showed, as previously mentioned, the property of phosphorescence and in this manner could be differentiated from the vibrios of *cholera indica*; but even those that were not luminous were only in part considered true cholera vibrios by R. Koch, in spite of the absence of actual methods of differentiation.

Pfeiffer started with the preliminary fact, that it is possible to confer a certain degree of immunity upon animals, used for experiment, by a preliminary treatment with true cholera vibrios, which, however, would only be effective in the case of actual cholera vibrios, not against other bacteria nor against the previously recognized cholera-like vibrios.

A serum is extracted from the blood of immunized animals which is mixed with cholera vibrios and injected into the abdominal cavity of guinea-pigs. The cholera vibrios perish within half an hour, while other vibrios are entirely

uninfluenced. This fact did not at once gain general recognition without raising some questions. Gruber subsequently showed that the immunized serum also acted upon the cholera vibrios in the test tube, causing a clumping (agglutination). The diagnosis of cholera is founded upon these observations. If cholera-like vibrios have been obtained in pure culture from the dejecta of a patient we proceed to differentiate.

1. *By testing the conglutination.* Three mgrm. of a fifteen hour old agar culture are carefully mixed in $\frac{1}{2}$ cc. bouillon. Then 20 mgrm. of serum from a guinea-pig, which has been highly immunized against the cholera vibrio, is mixed in $\frac{1}{2}$ cc. of sterilized bouillon and now both preparations are mingled in the same vessel. This mixture is at first uniformly turbid. If in a few minutes this turbidity becomes flocculent and in the course of an hour a precipitate forms, this reaction is greatly in favor of cholera vibrios. The same process may also be noted in the hanging drop. The vibrios lose their motility and clump in irregular heaps.

2. *By Pfeiffer's animal experiment with immunized serum.* Blood serum of guinea-pigs or goats that have been treated for months previously with cholera vibrios and thus have attained the highest possible degree of immunity, is greatly diluted with ordinary nutrient bouillon (in the proportion of 1:100). This mixture represents the reagent. A loop, which will only contain about 2 mgrm. of a twenty hour old agar culture of vibrios, that are to be tested, is uniformly distributed in 1 cc. of the just described bouillon-serum mixture, and the precipitate which results is injected into the abdominal cavity of young guinea-pigs, the animals weighing 200 grams. By means of fine, glass capillary tubes, which are inserted into the abdominal cavity, every five minutes a drop of fluid from the contents of the abdomen is obtained, examined in the hanging drop and also stained in a cover-glass preparation. True cholera bacteria during this investigation are transformed into peculiar, pale clumps, by the action of the cholera anti-bodies; these clumps are then dissolved by the fluids of the abdominal cavity and no residue is left. This process of dissolution, which takes place with the exactness of a chemical reaction, provided sufficient activity of the cholera serum is present, is completed in twenty minutes.

If after this period numerous, unchanged, motile vibrios are still detected in the tests of the peritoneal contents, they are positively not cholera vibrios, therefore a foreign variety of vibrios is present (negative reaction). If, on the other hand, all cholera bacilli are destroyed, two possibilities are present: either we are dealing with a true cholera culture, which has become specifically influenced by the bactericidal action of the cholera anti-bodies (positive reaction), or we are dealing with one of those saprophytic vibrio-cultures which are entirely devoid of all pathogenic properties and succumb to the anti-bacterial influences contained in the normal organism of the guinea-pig, in a brief time, even without a specific serum reaction. The decision is obtained from a control animal; one loop of the culture in question, in 1 cc. bouillon + 0.1 of normal serum being injected. If the vibrios are still motile and living in the control guinea-pig, during a period in which they are otherwise completely dissolved in a cholera-serum animal, then the true cholera nature of this variety of comma bacillus is to be regarded as proved.

If the diagnosis, cholera indica, has been made in a certain case, *special indications arise in regard to the general public: isolation of the patient, precaution against carrying the germs from the dejecta of the sick, the most explicit investigation of the source of infection, and the protection of the well against the dangers of infection and disease*; weighty problems, which all require circumspection, when the physician is called upon to act in an exposed locality. The physician, in private practice, is to a great extent exempt from these duties by the aid of the Boards of Health. At the conclusion of this article I shall give a brief (although not exhaustive) review of the hygienic and sanitary measures which are necessary under such circumstances.

Before considering the treatment of cholera I must touch upon an important experience in the study of cholera.

THE "GENIUS EPIDEMICUS"

The "genius epidemicus," a predisposition of a great number of the people to become ill with analogous or similar symptoms, is frequently spoken of. From a few isolated cases of influenza, of measles, of scarlatina, the "genius epidemicus" suddenly flares up an epidemic, quickly causes the number of cases of intestinal catarrh or bronchitis in a given population, to increase in a surprising manner. Two different elements may be considered as producing this condition; in the first place, disturbances in the bodily functions of many persons, by which the pathogenic agents find a suitable soil. A predisposition of this sort may occur in the autumn months, in which an inordinate use of fruit favors the development of intestinal bacteria, or a massing of persons who have not acquired immunity by recovering from the disease. Sudden changes in the weather may increase the predisposition. A second condition consists in the fact, that the causative agent of a certain disease *attains a high grade of development outside of the human body by favorable conditions of growth*. This latter circumstance must unquestionably be taken in consideration in the epidemic distribution of cholera indica.

It is of interest to note that in the years 1892 and 1893 many cases of severe *cholera nostras* arose simultaneously with *cholera indica*. Fürbringer was the first to call attention to this. The same observation was noted in 1886 upon the shores of the Rhine, during a small epidemic of cholera indica in Gonsenheim and Finthen. In 1892 and 1893 it might have been thought that these cases were true cholera but the most minute bacteriologic examination, even in fatal cases, showed the absence of the pathogenic agent of cholera indica. The previously described microorganisms, however, were found, of which the majority are known to be regular or occasional inhabitants of the human intestinal tract, without their presence constantly leading to disease. During the period just referred to, some of these microorganisms had to be considered as the cause of these severe affections. A number were introduced with the drinking-water, others with the food—but up to a certain point this is always the case. Although the drinking-water has been greatly improved in Hamburg since 1892, prior to this period the conditions were the same and in spite of this, cases of cholera nostras were of the greatest rarity. Berlin, Altona, and many other cities may be used as examples in the same sense. In

the years 1892 and 1893 the pathogenic agents of *endemic cholera* (*cholera nostras*) must have found a particularly favorable soil of development which showed itself, either in the amount or in the rich production of toxic substances. The circumstance, that toxic symptoms became so very prominent in the clinical manifestations of the affection favors the latter view and further proves that our endemic schizomycetes are capable of producing these toxic substances, under favorable conditions, which give character to the picture of cholera.

These interesting experiences may be a beautiful example that the "genius epidemicus" may depend upon the development of microorganisms, rich in toxins, the common varieties of which give rise to no, or but slight, symptoms upon being introduced into the human body. The experience that certain varieties of bacteria increase and decrease in virulence, also coincides with this view.

THE TREATMENT OF CHOLERA INDICA

The method of treatment has already been described in part. There are still, however, some points to be discussed. The attempt to treat cholera by intestinal antiseptics, by all methods that have been tried up to the present, has proved futile. Further, the treatment by *opium* must be considered; this can only be employed in those cases in which all suspicion of the toxic action of the cholera vibrios, with the exception of the diarrhea, is absent. In well developed cases of cholerine and cholera, evacuation of the intestinal canal is the first object in the treatment.

As reported by Lebert, Jules Guérin in 1849 treated all cases of cholerine with *castor oil*, and as the result of this, the same remedy was also much used in England. One or two tablespoonfuls, according to the age of the patient, are sufficient in the majority of cases.

Besides castor oil, calomel is to be considered, in the use of which the point has been emphasized, that a simultaneous anti-bacterial action takes place, by the splitting up of the drug into minimal quantities of corrosive sublimate. The employment of calomel in the therapy of cholera is not quite new. Reports of its use have been handed down to us by English physicians from the year 1830. In 1840 Amelung propounded the question: "Are small doses of calomel of use in cholera?" Toward the end of the fourth decade of the last century, finally the drug was particularly lauded, especially by the English, by Stedman, Allan, Allen, and Roger.

Further, Felix Niemeyer in the Magdeburg epidemic, v. Leyden in the Königsberg epidemic, made quite extensive use of calomel; v. Ziemssen also greatly praises the drug. The dose employed by various authors differs. Sometimes large single doses of 0.3–0.5 ($4\frac{1}{2}$ – $7\frac{1}{2}$ grains) are administered, three times, followed by smaller doses, at other times smaller doses of 0.03–0.05 ($\frac{1}{2}$ – $\frac{3}{4}$ gr.) only are given. Personally I prefer small doses, as large doses may readily give rise to symptoms of mercury poisoning. This treatment is continued from one to two days. As a rule, but slight increase of the diarrhea is noted. At first, the color is unchanged, a greenish discoloration being hardly noted, but often in the course of the succeeding day a yellow or brown color of the feces is observed. In this manner an adult receives *at most from 06–1*

gram of calomel in two to three days ($7\frac{1}{2}$ –15 grains). These doses, which must be decreased in the case of children, are sufficient to attain the object in view. Many trials with other purgatives did not give a satisfactory result.

Besides this treatment the employment of Cantani's *tannic acid enteroclysis* must be considered. Cantani introduced this method in the therapy of intestinal diseases in 1870 and employed it especially in cholera, as according to his experience the Neapolitan tanners suffered but little or not at all during cholera epidemics, while in tanneries in which tannic acid was not employed, as in the tanning of leather for gloves, the workmen suffered severely. He considered the effect of the *enteroclysis* to consist in the fluid comparatively frequently passing the ileo-cecal valve, thus reaching the small intestine where it unfolded a disinfecting and astringent action, a view that was confirmed by the experiments of Manfredi and De Simone who showed that tannic acid has an injurious action upon comma bacilli.

According to Cantani, 1–2 litres of a 1 per cent. solution of tannic acid at a temperature of 39° – 40° C. (102.2° – 104° F.), is allowed to flow through the irrigator into the rectum, this procedure being repeated several times during the day. I should like to add, from my own experience, that it is well to use but little pressure and permit but a very slow flow. It is then often possible to reach beyond the ileo-cecal valve and influence the small intestine. However, the number of such cases does not appear to me to be very great. Often the fluid is rapidly discharged after its entrance and it is impossible in spite of the greatest care to introduce copious amounts into the rectum. Nevertheless the effect cannot be denied. In many cases the bowel is quieted, either by means of the action of the tannic acid or of the warmth of the fluid; in some cases a decided improvement in the cardiac action could be noted, so that the method may be recommended as practical and as one easily utilized. The attempts instituted by us, to substitute other drugs for tannic acid, had no more result than Lustig's experiments in the cholera epidemic in Triest in the year 1886.

Lately, v. Genersich has devised a method which he terms "*diaclysmos*," by which the digestive canal, by way of the rectum, is flooded by much larger quantities of fluid (5–15 litres of a 1–2 per cent. solution of tannic acid). He has tried this method in several cases and advises it. The fluid is warmed to a temperature of from 38° – 40° C., a pressure of 80–100 cc. is applied, the anus being firmly squeezed around the insertion of the tube. The flow is interrupted from time to time, provided it is uncomfortable to the patient, but may be continued after a brief interval. After some time copious vomiting of the fluid irrigated through the bowel is said to result. If the irrigator is now removed a large quantity of fluid flows out, but from 1–2 litres are retained. v. Genersich's results are certainly worthy of note and in the next epidemic this modification and amplification of Cantani's enteroclysis should certainly be attempted. Whether it will be advisable in every case, to use these injections with very high pressure, must remain to be decided.

Cantani's advice, to employ enteroclysis in an early stage and to reapply the process for a few days with the reappearance of diarrhea, certainly deserves the fullest observation. The preliminary diarrhea, particularly requires careful treatment as the main point in the treatment of cholera is

here to be observed. For this reason it is well, as particularly emphasized by v. Ziemssen, that in an epidemic of cholera, the physician should constantly have at hand all the apparatus for tannic acid enteroclysis so that no valuable time is lost. It is true, even with the employment of Cantani's tannic acid enteroclysis, it cannot be avoided, that some cases of cholera-diarrhea enter upon the algid stage or become severe attacks.

A symptom which we have learned to be extraordinarily troublesome is

VOMITING

Medicine is administered to the patient, or to allay the intense thirst some water, tea, or wine is given. The patient drinks eagerly, but after a few seconds, vomiting regurgitates the fluid from the stomach, and not only this, but even additional quantities of fluid, often having a yellow or brown color. Under these circumstances it is particularly difficult to administer drugs by the mouth. In many cases it would be well to empty the bowel with *calomel* or some other purgative, but the vomiting causes these efforts to become futile. In some few cases, it is possible, by the use of *small pellets of ice*, which the patient swallows, to allay this condition, in other instances it is necessary to resort to the use of *narcotics*. A hypodermic of morphia ($\frac{1}{12}$ gr. and more) is very useful in such cases; it allays spasm and vomiting, and what is at least as important, it has a quieting effect upon the subjective sensations. The *subcutaneous injection of extract. opii aquos. liq.* (15 drops) may be employed for the same purpose. In itself, vomiting is perhaps not such a serious symptom, for the researches from Hitzig's Clinic (Alt), have shown that a toxic substance is secreted in the stomach and by the act of vomiting the poison may be discharged.

Under these circumstances, the thought will arise that we must follow the method indicated by nature, especially as it cannot be gainsaid that some cases, in spite of profuse vomiting, are not prevented from retaining some fluid, although most of it is immediately rejected; some of these cases recover. Naturally it must be remembered that such cases are most often individuals with powerful resistance. With this point in view, during the great epidemic of 1892, we performed lavage of the stomach, with the hope of preventing the excretion of the cholera toxins and thus removing them from the body.

The results, at that time, were not particularly brilliant. Perhaps we expected too much from the method and after a few trials, in which the results were not very marked, the treatment was abandoned. The results in the small epidemic of 1893 were decidedly better and in a few cases, after repeated lavage, even surprising. But it is always hazardous to draw general conclusions from a few observations. There are no therapeutic measures by which we may hope to neutralize the poison in severe cases, if we do not ascribe such an effect to the enteroclysis of tannic acid.

Other methods, to neutralize the poison in the body, will have to be discovered in connection with experimental investigations. It will be the object of bacteriologic investigation to discover agents, which either form harmless combinations with toxins that result from the cholera process, or that destroy

them. If such substances are found, and their introduction into the human body is found to be without deleterious consequences, a subcutaneous injection, as well as their use by way of the bowel may be attempted.

In 1892, experimental bacteriology furnished us with a product of this nature, *anticholerine*, discovered by Klebs. This substance has not as yet furnished unquestioned results, although trials with the substance should be continued. Lately Kitasato in Japan, has prepared a *cholera-antitoxin* which was used by Na Kagawa in 193 positive cases of cholera (determined bacteriologically). The mortality, as the result of this therapy, is said to have been much reduced. Urticaria, arthralgia and myalgia have been observed as secondary effects of this medicament.

The *hot bath*, 32°–34° R. (104°–109° F.), is utilized in the treatment of cholera, by means of which an excretion of toxic substances by the skin and an influence upon the temperature and circulation may be hoped for. The first sensations produced by a bath of this kind are not always pleasant; but after a little time the beneficial effect will be grateful to many patients. The difficulty in respiration, as well as the spasms, frequently desist after a hot bath, and this is so grateful to the patient that many, after a short interval, request another hot bath.

This favorable action does not occur in all patients, in some the pulse does not improve and *attacks of syncope* are superadded to any attempt at giving a prolonged hot bath. Similar results were witnessed by Baelz in the employment of the hot bath in Japan, a method which is quite common in the treatment of cholera in that country. In favorable cases a cholera-exanthem arises and with the cessation of the cramps, permanent disappearance of the bluish-gray color and a permanent rise of the pulse, convalescence is ushered in. Naturally the hot bath may be frequently repeated.

Perhaps the effect of the hot bath may even be increased, by the addition of from 100 to 200 grams of ground mustard, following Trousseau's process, in *cholera infantum*. Hot-air baths, steam baths and sweat baths in place of the hot bath, followed by enveloping the patient in woolen blankets, have given less satisfactory results.

The exponents of hydrotherapy have recommended another process. Powerful rubbing of the cutaneous surfaces by means of a sheet dipped in cold water (below 60° F.); this is continued until the skin becomes reddened and simultaneously, every two minutes, about 10 litres of cold water are poured over the head. Immediately afterward, the patient is placed in the warmed bed, well covered with blankets, a hot water bag is applied to the feet and every half hour a fresh, cold compress is applied to the abdomen. Fresh drinking-water is given as often as asked. If no perspiration has appeared after three hours, this entire process is to be repeated; should it occur sooner the interval may be six hours and only five minutes need be employed in friction, at a temperature of 64° F. While the patient is in bed, he is to have a plentiful supply of fresh air. In the epidemic in Hamburg, so far as I know, this process was not utilized. Casper places his patients in a warm bath (93° F.) and has ice-cold water poured over them; this may be looked upon as a very powerful stimulant. Romberg treated 20 patients in this manner with a mortality of 55 per cent., a result which cannot be regarded

as particularly favorable and is not calculated to increase the enthusiasm of inspired hydrotherapeutists.

A prominent part, in this stage, is played by the *administration of fluid*. Although the loss which the body suffers from the diarrhea, is not as great as was sometimes assumed, nevertheless the thirst of the patient shows that the organism requires fluid.

As larger quantities are soon vomited it is advisable to give only small amounts, a tablespoonful or even a teaspoonful at a time. *Hot drinks* are most suitable, as they are rapidly absorbed, such as *hot coffee* or *hot tea*. But it is well to also consult the wishes of the patient, as variable as they may be. If we are successful in allaying the thirst in one with hot drinks, another will desire cold water or ice. It is common practice to administer *alcohol*, in the form of wine or grog. In small quantities, this procedure is not dangerous; larger amounts of alcohol, according to our experience, have a detrimental action. Of actual nourishment, in this stage there can naturally be no thought.

In all of these cases a *careful control of the pulse* is necessary. If it becomes small or imperceptible, or if the second sound of the heart disappears, it will only rarely be possible, by employment of the hot bath or the administration of hot fluid, either by mouth or by rectum, to improve the circulation. By hypodermics of oil of camphor, of which frequent use should be made in a threatening algid stage, this condition is not much improved. The physician must now have recourse to *subcutaneous or intravenous infusions of normal salt solution* to stimulate cardiac activity, as was previously described.

Which of these methods is to be preferred, is as yet undecided. The greater risks, which were previously ascribed to intravenous infusion, are not present in a modern hospital. Intravenous infusion is unquestionably the older of the methods, although it appears to have fallen into neglect, prior to the Hamburg epidemic. In the epidemic of 1831-32, of the English physicians, Doctor Thomas Latta treated 6 cases and McKintosh 156 cases in this manner. Following them, Hayem and later P. Guttman employed intravenous infusion. But on account of the slight result, some authors advised against its employment. We were justified in making an extensive use of the method in Hamburg on account of the introduction of antiseptic surgery, which was unknown in the previous trials of this method. It must be added, that in the algid stage of cholera, the opening of a vein and the introduction of a cannula offers no more difficulty than the same operation upon the cadaver. I must state here, that damage to a patient by this operation has hardly been observed. The majority of those physicians who have had an opportunity of watching the results, will understand the astonishing effects of this treatment and I need not enter into further detail. But I must not conceal, that in some instances, the good results may not appear or may be only transitory. Of especial importance, however, which I should like to emphasize again, is the point, that the fluid to be injected is to be of a *higher temperature than that of the body*.

If favorable results do not appear, a *second* and later a *third* and even a *fourth* infusion should be given; up to 4-6 litres (in individual cases, even

more) of a 0.6 per cent. sodium chlorid solution have been injected into some patients, in the course of the disease—not always, but frequently enough with apparently permanent results. But some of these apparently cured patients, later died in coma. The employment of stronger normal salt solutions, as advised by Gärtner and Beck, gave no better results.

In place of intravenous infusion, Cantani introduced subcutaneous infusion in the therapy of cholera, after Michael in 1883 and, later, Samuel had advised this method. Cantani used a solution which contained 4.0 grams sodium chlorate and 3.0 grams sodium carbonate in a litre of water. Of this solution 1–1½ litres, at a temperature of 100.4°–104° F., were injected, at two or three places, about ½ litre at each point, in the two ileo-cecal regions or in the region of both glutæi. The most suitable points, according to Cantani, are the ileo-cecal regions, the fine end of the needle being directed toward the abdominal wall. The abdominal skin, in fact, is very suitable for these infusions, and with Cantani, I should advise that the *hypodermoclysis* be performed simultaneously at two points. Tubes with two cannulas and trocars may easily be arranged. The region of the neck must be designated as entirely unsuitable for these infusions.

It is difficult to decide as to the preferable method. In general subcutaneous infusion is most often employed earlier than the intravenous. This is perhaps also the reason why Hager, from investigation in the Old General Hospital in the wards of Dr. Jollasse, prefers the subcutaneous to the intravenous method. Nevertheless the proportional percentage of the definitely cured by intravenous infusion is not so great that a decided preference over the subcutaneous method may be concluded. Intravenous infusion should be preferred, above all, in those cases where, by a rapid and *transitory* restoration of the circulation, a hope of maintaining life is present. *In all other cases subcutaneous infusion may take the place of intravenous.*

It is to be hoped that the proposal to introduce the fluid into the abdominal cavity or into the pleural sacs will only remain a proposition.

The treatment of the *comatose stage* or of cholera typhoid cannot be designated as satisfactory. Milder cases, in which there is only slight somnolence, with or without fever, frequently run a favorable course without any treatment.

In severe cases, the use of warm or hot baths (up to 96° F.) or mustard baths followed by subsequent wrappings in woolen blankets, or by a “sitzbath” in bed, must be employed to obtain derivation by the skin and this must be increased by the intake of plentiful amounts of milk and water; however, the prognosis in the severe cases is always unfavorable. It has occasionally been attempted, in this stage, to employ venesection, or to combine this with succeeding intravenous infusion of a physiologic salt solution, to produce a dilution of the toxic substances present in the circulation, or even to directly eliminate a portion of them. The result was not in keeping with the expectations. In a case of coma during cholera nostras, Rumpel attempted to introduce larger quantities of an alkaline fluid into the stomach, by means of the stomach tube, in order to produce a more rapid neutralization of the poison by stimulating diuresis. There would be no objections to a trial of this sort in cholera indica.

Endeavors have also been made to bring about a more profuse diuresis by the use of potassium acetate, diuretin and digitalis, so as to neutralize the toxins. However, this procedure is devoid of the correct foundation, for frequently there is a profuse excretion of urine in coma, or in spite of a plentiful excretion of urine, coma arises. In disease of the renal secretory epithelium, which is usually severe, it is not surprising that the employment of diuretics remains without result. Therefore, with v. Ziemssen, I desire to warn against their employment. As the poison is quite unknown which produces the comatose stage, it is not to be considered, for the present, that a neutralization or destruction inside the organism is possible.

A detailed description of the treatment of the *complications* would lead us too far.

The chronic affections of the intestine, which occur in connection with cholera, require very careful treatment. These usually run their course with a continuance of the watery diarrhea (as a rule, without comma bacilli) and complete anorexia, conditions which result in emaciation, and with a high degree of weakness; the cause of these must be referred, for a great part, to a severe implication of the bowel and may in feeble individuals be the direct cause of death. In other cases, invalidism, lasting for months, is the result. For these reasons, these affections require careful attention on the part of the physician. Patients of this kind had better be kept in bed. In some of our cases, the continuance and aggravation of this condition could be directly ascribed to premature leaving of the bed. Then, care in the choice of food is necessary. In this respect milk occupies the first place, the choice of which, as a food, in such instances has received a further theoretical support, by its faculty of limiting intestinal decomposition, which has lately been determined. In patients that cannot take milk, even with the addition of minimal quantities of brandy, cocoa may be tried.

Besides this, soups of oatmeal or barleymeal with red wine, are useful. Of solid food it is advisable to begin with roasted fowl, chopped or roasted beef, mashed potatoes or rice, and only very gradually to enlarge the bill of fare. Carbohydrates, particularly bread, are to be avoided for a long time and the same is true of cooked eggs. Great care must be exercised, for a long time, with the so-called "sweet foods." Cases in which the diarrhea has given way to constipation may take rice and baked apples. It is well to exercise caution and to allow only such stewed fruit as contain tannin, which nevertheless are easily digestible. In this sense cranberries may be given, which may always be obtained dry; before they are prepared they should be placed for twenty-four hours in water. An auxiliary in this diet is a good, mild, but tart red wine. The tannic acid, which such a wine contains, has a favorable influence. Under all circumstances, the wine is to be given in small quantities. If improvement occurs, the bill of fare may gradually be extended. In most patients it is of advantage to favor the circulation of the blood in the abdomen. This may best be attained by the use of Priessnitz's compresses, which should either be worn constantly or only at night. During the day a woolen bandage may take its place; after the warm, moist compress has been removed, the abdomen is to have a cool rubbing followed by substantial friction.

Among drugs, opium, or opium and bismuth are best:

℞ Opii	0.015
Bismuth. subnitr.	0.3

One powder three times daily, or the combination advised by Wunderlich:

℞ Opii	0.025
Acid. tannic	0.05
Sacchar. lact.	0.5

M. D. tal. dos. No. 10. One powder three times daily.

Bismuth alone frequently acts well, but then larger doses must be employed, such as are used in the treatment of gastric ulcer, and have lately been recommended by Kussmaul and Fleiner. I have frequently given 1.5–3.0 (gr. 23–46), in wafer, three times daily with good results; v. Ziemssen recommends bitter tonics and combinations of bitters, such as have an influence upon intestinal digestion and peristalsis, if diarrhea and constipation alternate during convalescence. First to be mentioned in this respect are the preparations of rhubarb root. In diarrhea with a tendency to flatulence, small doses are useful in the manner proposed by Ziemssen:

℞ Tinctur. rhei aquos.,	} āā.....	30.0
Elixir. aurant. comp.,		

M. D. S.: A teaspoonful two to three times daily.

In constipation, v. Ziemssen advocates tinctura rhei vinosa, either pure or with elixir. aurant. comp. and tinct. chinæ comp. in doses of a teaspoonful. The same results may be attained by an infusion of rhubarb:

℞ Infus. rad. rhei (1–2).....	120.0
Syr. aurant. cort.	30.0

M. D. S.: A tablespoonful every two hours.

But there are cases, which in spite of the most careful hygiene in regard to diet and mode of life, do not improve. Rumbling in the abdomen, constipation alternating with diarrhea, do not cease, so that nutrition and the psychological condition of the patient begins to suffer. In instances of this kind, it is well to remove the patient from his surroundings; in these cases, v. Ziemssen advises a change of climate, either a mild mountain climate, or a warm climate for the winter. I have seen good results follow a residence in Italy and I refer this more to the favorable effect upon the nervous functions than to a form of treatment. Advice of this kind must be made to depend upon the season. A so-called soothing climate is to be preferred to a bracing one, particularly is a climate to be chosen which does not offer too great a resistance to the heat production of the patient.

The coasts of the North Sea for this reason are less beneficial than the mountains and in a cold season a residence in the South is to be preferred to the mountains.

[See also Serum Therapy, page 909.]

THE PLAGUE, THE BUBONIC PLAGUE, THE PEST

By W. KOLLE, BERLIN

THE plague, which lately has had the attention of physicians and hygienists of the whole world directed to it, is one of those pestilences of which we possess authentic historic records from the most ancient times. Even in ancient times it had visited the various countries and parts of the earth in so destructive a manner, that it is even possible to-day to determine from the descriptions which have come down to us how in fact centuries before Christ *true oriental bubonic pest* was the scourge of mankind. It is not my intention to investigate whether all of the great epidemics, of which we have reports, thus for example, the pest of Thucydides in Athens, were actually true bubonic plague. From the enormous literature which has survived, regarding the most terrifying pestilence of antiquity and of the middle ages, the critical medical historian will be compelled to exclude much which was regarded as pest by terrified and imaginative physicians and laymen and which must be ascribed to other causes. As voluminous as the literature of the black death of the middle ages is, for the physician it offers but little that is of value for it contains but few scientific, tangible or certain data with the exception of a few clinical and epidemiologic facts. Only in the middle of the last century did the great German clinician and epidemiologist, Griesinger, give such a true and objectively scientific picture of the plague, which he had combined for the most part from descriptions of recent observations of his own, that it is worth while to repeat his description of the chief symptoms of the pest in this article (see page 739). Clot-Bey, the great Franco-Egyptian physician, about the beginning and middle of the last century, brought about a decided change in the conception of the nature of pest by his studies, which he attempted to found, in a scientific manner, upon the views of the nature and symptoms of pest existing at that time. But in all of these descriptions the solid foundation, which was only produced by the discovery of the exciting cause of pest, was missing.

In the last decade of the past century, there were several opportunities of observing this scourge of the human race by the modern methods of bacteriologic and clinical investigation. After an apparent quiescence, which had stamped the disease as exotic, as far as Europe was concerned, in the last few years the plague again entered the portals of that continent. Previously upon its outbreak in Hongkong (1893-1894), since which time the latest epidemics date their spread westward, two bacteriologists, educated in Europe, Kitasato, a pupil of R. Koch's, and Yersin, a pupil of Pasteur's, independently of each other, succeeded in discovering the generator of plague and thus founded the basis for a rational study of the pestilence.

When the plague appeared in Bombay in 1896 and the eyes of Europe were directed to the threatening danger, on account of the enormous distribution which the disease attained in that city, several countries decided to equip scientific commissions to be sent to India to investigate the disease. Although a comparatively small number of physicians, belonging to the German, Austrian, Russian and Egyptian plague commissions, had an opportunity of instituting detailed studies during a few months, we nevertheless possess enough facts in the rich, scientific material examined by the members of these commissions in India, as well as from the investigations of Yersin, Kitasato and Aoyama and others in Hongkong, to justify the presentation of a new picture of plague, from a clinical, bacteriologic, pathologic and epidemiologic point of view. In estimating the value of the results accumulated in so short a time by the Pest Expedition sent to India, it must not be forgotten that this commission consisted of the ablest investigators, pioneers in the realm of infectious diseases, to whom the study of the bubonic plague was entrusted, that among them were men such as R. Koch, Gaffky, R. Pfeiffer, Weichselbaum, Bitter, Sticker, Dieudonné and others.

ETIOLOGY

The *cause of plague* is the *bacillus* discovered by Kitasato and Yersin. There can be no doubt, to-day, of its specific nature. Wherever over the earth, whether in Asia, Europe, America, Australia or Africa, the plague has been carried in the course of the last years, everywhere the *specific plague bacillus* has always been found. Up to the present it has not been found in normal individuals nor in persons suffering from other diseases, and the numerous animal experiments conducted with it have shown that the same pathologic phenomena produced in man are developed in different animals with pure cultures of bacteria which have been transplanted through many generations. The finding of specific changes in the blood of animals that have been immunized with plague bacteria, and the appearance of specific protective bodies in the blood of human beings who have recovered from the disease, are incontrovertible arguments that the small, pole-stained rods, from the class of chicken-cholera bacteria, are the sole cause of oriental, bubonic plague.

Regarding an accurate description of the morphology and biology of the bacillus of plague, as well as of the numerous animal experiments conducted with it, the reader is referred to the detailed reports of the German, Austrian and Egyptian plague commissions, as well as to the numerous reports of the Pasteur Institute and from other laboratories that have busied themselves with the study of the bacillus of plague.

Here only a brief sketch of the essential features in the bacteriology of the plague bacillus can be given.

BACTERIOLOGY

The plague bacillus represents a small, immotile rod, which upon suitable staining in the animal tissues and in culture media, is more intensely stained at the poles than in the center. The best method of demonstrating this so-called *pole staining*, which is common to the group of chicken-cholera bacteria, is that of Sobernheim, fixing the preparation in absolute alcohol with succeeding rapid evaporation of the alcohol in the vicinity of a flame. The bacillus grows upon all of the ordinary culture media, best

upon agar that is slightly alkaline. There it forms peculiar, granular colonies which particularly upon dry agar frequently reveal the formation of a delicate, transparent border surrounding a button-like stained center, a characteristic which may be utilized in the recognition of colonies as plague bacilli. The bacillus grows best at a temperature between 25° C. and 30° C., the limit of growth being 40° C. and about 5° C. It does not coagulate milk. In every culture two kinds of colonies are found, smaller and larger ones; if one kind is isolated, from each separately both varieties develop. They show no differences in virulence. The plague bacillus is not very resistant to drying; complete drying destroys it in the course of a few, at most twenty-four, hours. Neither are high temperatures well borne by the bacillus; temperatures of 60° C. for one hour destroy it in the course of a few hours. In the presence of saprophytic bacteria, the pest bacilli succumb very rapidly, particularly as they develop but feeble growth energy as saprophytes. The bacillus is not very resistant to disinfectants. The bacteria perish in twelve minutes from the action of 1 per cent. carbolic acid solution, in a 1-100 solution of corrosive sublimate after a few seconds, in a $\frac{1}{2}$ per cent. caustic lime solution in twenty minutes. Milk of lime will sterilize feces containing plague bacilli in from one to two hours if the mixture has an alkaline reaction. The mineral acids are particularly effective. A 1-1000 hydrochloric acid solution kills the bacillus in half an hour, 1-500 sulphuric acid solution in five minutes. In the human secretion the pest bacilli are readily destroyed, either at boiling temperatures (sputum) or by acids (feces with common sulphuric acid). The virulence of the bacilli varies greatly. In the animal experiment, particularly in rats, it is noted that not only the cultures which are grown from the cadaver show a decided difference in virulence, it is also observed, that cultures, without our being able to assign a reason, after but few transplantations to artificial culture media, even in cultivation from animal to animal, frequently lose their virulence. Some original cultures, on the other hand, retain their virulence very well, it being even possible to increase it by cultivation from animal to animal.

The toxins of the plague bacilli are unquestionably contained in the body of the bacteria, as was first demonstrated by R. Pfeiffer. A fact that deserves special observation is this, that frequently after an injection of inanimate plague cultures, even when the first injection has been well borne, marasmus occurs later in the animal. The filtrates of bouillon culture have not been found toxic by all observers. The conditions in cultures of this kind may be similar to those of enteric fever and cholera, where in older cultures an extraction of the body of the bacterium occurs and thus a passage of the toxins takes place—even though they be only secondary, the so-called toxoids (in support of Ehrlich's nomenclature of the toxins which develop and are demonstrable in old bouillon diphtheria cultures by conversion of the primary diphtheria toxin).

To test the pathogenic property, the most suitable animals are rats, guinea-pigs, mice, rabbits, monkeys and cats. The introduction of the smallest amounts of the bacterial culture in any of these animals leads to death after the formation of buboes followed by sepsis. After feeding material obtained from plague patients most rodents, especially rats, succumbed.

The test in guinea-pigs has particular importance for diagnostic purposes. Weichselbaum, Albrecht and Ghon, have found that the application of plague bacteria to the shaved abdominal skin produces a very typical picture of plague. Small nodules develop upon the area at which the plague bacilli were applied and, under the formation of a bubo and white nodules in the spleen, in four to six days after inoculation, death occurs. Even very old cultures, in this method of application prove pathogenic in animals, and with this process it is possible, even where there are mixtures of bacteria in which there are but few plague bacilli, for example, in feces, decomposing fluids, etc., to demonstrate plague bacilli.

CLINICAL PICTURE

The development of a typical clinical picture is best conveyed by the previously mentioned classic portrayal of Griesinger. "Rarely are prodromes present, anorexia, pains in the small of the back, lassitude, malaise. Usually the outbreak is abrupt and sudden, with a stage of depression or a more or

less well defined collapse, which appears to belong to the primary action of the toxin. The patients are greatly debilitated. They suffer from severe dull headache, vertigo and a weight in the head, which is often compared to the action of strong coal gas. The pale, relaxed face, the dull, hollow eyes, the empty, rigid expression, the heavy, stuttering speech, the vacillating gait, the dulness of the senses and of the mind, early give the patient the appearance of being under the influence of alcohol, if these symptoms of invasion are at all strongly developed. There is often nausea and frequently vomiting and the patient suffers from transitory tremor with a feeling of internal heat or actual chill; the pulse is but slightly increased and soft, often small and irregular. Frequently at this early period there is injection of the conjunctiva at the internal canthus of the eye, dilatation of the pupils and entire distortion of the face. This first group of symptoms is occasionally only indicated and lasts but a few hours; frequently it is markedly developed and lasts an entire day, often up to three days.

“The onset of the fever characterizes the further development of the disease. The patients become restless, the skin soon burning hot, the face somewhat congested, the eye injected, brilliant but staring, the pupils for the most part are dilated; there is dulness of hearing; the lips, and the tongue which shows a coating as white as chalk, swell and soon become dry. Painful sensations of heat in the epigastrium and hypochondrium are not quieted by eager drinking of cold fluid. The patients are so devoid of strength and so somnolent that even if the mind is clear they are scarcely capable of answering questions. Some point to the head and the region of the stomach as the seat of pain and then appear exhausted from the exertion. The severe headache gradually changes into stupor and delirium and in the severe cases, upon the second to the third day of the disease, there is a well developed *status typhosus* with complete prostration. The vomiting continues, the urine is very scant, often hemorrhagic, or even entirely suppressed; there is often some bronchitis, frequently also epistaxis. From the second to the fourth day of the disease a bubo appears in the inguinal region accompanied by pain. The bubo may also occur in the axilla, in the neck or at the angle of the lower jaw. There may be several or only one; they may be small or large from the onset. Carbuncles are rarer, they usually occur after the bubo, occasionally, however, without this; they develop most frequently upon the legs, upon the neck or upon the back. With the formation and further development of these localizations, in a favorable course, a cessation of the fever occurs, ushered in by marked sweating. The patient becomes more quiet, the facial expression more natural, the tongue moist, the injection of the eye and dilatation of the pupil decrease. The buboes develop further, suppurate, or disappear. The carbuncles are limited, the gangrenous portion is desquamated and, in favorable cases, with profuse secretion from the skin and from the kidneys, improvement occurs, so that convalescence begins from the sixth to the eighth day of the disease.

“But not only during the time of the development of the localization does the remission occasionally not occur, but a *status typhosus* with sordes, low muttering delirium and diarrhea continues up to the fifteenth to the twentieth day of the disease, and even after a distinct remission a second stage with

irregular febrile paroxysms, formation of parotid bubo and miliaria may develop (without doubt pyemia). Death may occur at any time during the entire course, sometimes in the form of an unexpected sudden collapse, at other times with rapidly appearing convulsions and coma; sometimes with the signs of exhaustion, due to the intensity of the fever; occasionally from the development of an early or late septic condition (petechiæ, hemorrhages and formation of gangrene in the bubo). Convalescence sometimes is quite rapid. In many other cases great debility remains for a long time. Local disturbances, continuous abscesses which will not heal, suppuration of internal lymph glands, and the like, continue."

In the main, the observations of the scientific expedition have confirmed this classic description of the clinical picture. In individual points it has even broadened it. In the following, I do not intend to enter into individualities regarding the clinical course of the plague, as excellent descriptions of this disease have been published, among others in Nothnagel's Handbook of Special Pathology and Therapy in which the monograph on plague was written by Dr. Müller, the unfortunate investigator who himself succumbed to the pestilence in Vienna in 1898, and by Dr. R. Pösch.¹

The most important point which has cleared the many-sidedness of the clinical phenomena of plague, as described by Griesinger, and also accepted by him, is above all the constant connection between the bacteriologic, pathologico-anatomic and clinical modes of investigation. Only by the most minute examination of living plague patients, as well as of the organs at the autopsy and the search for the pathogenic agent in the morbid products, in the blood, in the glands, in the secretions, for example in the secretions from the lung, during life as well as after death, has it been made possible to divide the cases of plague into *two groups*, in the form of the *bubonic or glandular plague*, on the one hand, and *pulmonary plague* on the other. As a third form, *cutaneous plague* might be assumed. As, however, the reports are not unanimous, whether there is a primary localization of the plague bacterium in the skin, and also as the occurrence of plague phenomena upon the skin without enlargement of the glands, belongs to the greatest rarity, it is advisable to consider only *cutaneous plague* in connection with *bubonic plague*.

The most important point in the *clinical division* of the varieties of plague is the *principle of primary localization*, the importance of which was even recognized by Virchow, many years ago. It is clear from the onset that when we speak of a primary localization we must have points of support, why a localization of plague bacteria—for we are always concerned with these and the resulting change in the tissues—in the one case is *primary* and in the other case is designated as *secondary*. It may now be taken for granted that we have succeeded in discovering definite points of proof that there are *primary* as well as *secondary glandular swellings*, in an analogous manner as there are *primary* and *secondary plague pneumonias*.

¹ See also Sticker's article in the report of the German Pest Commission, as well as H. Bitter, H. Pinching-Bey, Report on Plague in Egypt, 1899–1900. Report of the Commission sent by the Egyptian Government, etc., and Aoyama, Report of the Imperial Japanese Academy, 1895.

The pathologico-anatomic picture and also the clinical course in both cases is entirely different, so that it will always be possible to refer glandular enlargements or pneumonias to one or the other group. Although Griesinger and also other authors regarded the appearance of plague without buboes as possible, that is, the existence of a primary blood infection, to which only secondarily the plague bubo or a pulmonary affection was added, the investigations of the Commission were not able to confirm this. We now know that in many cases of true bubonic plague the enlargement of the lymph glands may be so small that they may escape the observation of the examining physician while the patient is in the hospital. In other cases the primary seat is found to be in deeply situated glands, which are not susceptible of observation, or in the tonsils, in which the process, as a plague process, is not correctly recognized. And, finally, it has become clear since Childe's discovery, regarding plague pneumonia, that cases of plague may run their course as pulmonary inflammations and terminate fatally without the palpable glands of the body being implicated. In the cases from the older literature, in which during an epidemic of plague, many persons succumbed with the symptoms of plague without glandular enlargement, it is most probable that these cases were pulmonary plague. We now know that the *blood infections*, which since the report of Griesinger, and according to the pathological views of his time were correspondingly assumed to be primary, are always of a *secondary* nature. Blood infection may be added to each of the two plague varieties, to pulmonary plague as well as to glandular plague; the proof of this infection of the blood with plague bacilli has been frequently determined by bacteriologic methods as well as by the examination of the blood by culture. Numerous autopsies have also proven that in plague there is a constant local affection, either in the glands (skin) or in the lungs, in the cases in which there is blood infection, that, however, these local affections may also exist and lead to the death of the individual without a blood infection, a general plague sepsis having occurred.

After a larger plague epidemic had occurred in Oporto in 1900 and also in the same year a small epidemic occurred in Glasgow and a few cases having been brought into Germany in the year 1900, it will certainly be considered necessary that all physicians, especially those practising in coast countries, should become familiar with the clinical symptoms of plague. By this it is not to be assumed that the clinical observation of a case will always make it possible to make a diagnosis of plague with certainty. On the contrary, observations have proven that not only in cases of bubonic plague but particularly in cases of pulmonary plague, *a positive diagnosis is impossible without a bacteriologic investigation*. This is not only true during the course of an epidemic, but above all things in the first cases, which most commonly occur in seaport towns. Even careful and experienced physicians, in such cases, will not always find it possible to decide alone from the clinical picture regarding the differential diagnosis. Whether, for example, in mild cases (*pestis ambulans seu minor*), a glandular enlargement is of a venereal or an inflammatory nature or produced by the invasion and cultivation of plague bacteria. This is much more the case in pneumonia. The more accurately, however, the physician is acquainted with all the details of clinical observation,

the sooner will he certainly in suspicious cases have his attention drawn to the suspicion of plague and thus, by an early notification of the authorities and bacteriological institutes, be in a position to prevent the furtherance of the infection.

As Griesinger has already said, in the majority of cases the disease begins with a chill, suddenly, while the patient is in complete health, without premonition, without conspicuous prodromal symptoms, after a *period of incubation* which in general may be assumed to be from *three to four days*, but in individual cases may be as long as *six to eight days*; only very rarely will it be necessary to assume a period of incubation of longer than *ten days*. In individual cases, during this period of incubation, symptoms arise such as occur in other infectious diseases, pains in the limbs, some headache, lassitude, debility and disturbances on the part of the digestive apparatus. But in the majority of cases the patients, after having been attacked by a severe chill in complete health, in a very brief time present the appearance of severe illness. Not always, but in many cases, even during the last epidemic of plague, the reports of a *facies pestica* have again been noted, and without doubt it may be looked upon as an expression of the early intoxication, when patients show in their faces the expression of fear from which they suffer without there being anything demonstrable in them besides the fever and a painful glandular enlargement. This intense intoxication which is due to the plague bacteria as we already know, may also be seen in a very brief time from other symptoms, a typhoid *condition of the senses*, *severe headache*, such as frequently is only found in cerebral tumors, *disturbances of speech*, *sensations of vertigo* and *an implication of the cardiac activity*, which will be referred to more in detail later on. The *lalling speech*, which resembles that of an intoxicated person, is of diagnostic value.

The *fever curves* in plague cannot be designated as characteristic. From the great number of temperature charts which have been obtained and published during the Indo-Chinese plague epidemic, a definite law regarding the course of the fever cannot be constructed. The fever usually begins with an abrupt rise, remaining at a moderate height, with a remission lasting several hours during the morning for a few days, then with an increase in the remission the fever becomes normal. In some cases, after the fever has been sub-continuous, the defervescence occurs by crisis; in other cases defervescence occurs by lysis, which reminds us of the temperature curve during the third week of enteric fever. Occasionally the temperature shows the tendency to assume hyperpyretic ranges; in other cases the temperature does not rise beyond 102.2° F. Agonal temperatures are occasionally noted of 105.8° F. Subnormal temperatures, except in those cases in which collapse occurs, which terminate in death, are not noted. The duration of the fever may be from five to thirty days in cases which terminate in recovery. Not rarely, especially in such plague cases in which an early defervescence has occurred, after a period of a few afebrile days, an exacerbation occurs, which must be looked upon as the *fever of absorption*, as it goes hand in hand with a decrease in the size of the gland. With the absorption of the substance contained in the gland, the toxins present in the plague bacteria gain access to the circulation anew. Those cases must naturally be sharply

separated from the actual fever curve of plague in which, after the plague has run its course, a true suppurative fever occurs, such as we see in *streptococci* and *staphylococci infections*, which shows itself by a zigzag form in the fever curve, deep remissions in connection with the finding of streptococci in the suppurating glands or in the blood. We are then no longer dealing with the plague infection alone, but with a *mixed infection*, which may occur in quite a similar manner as in other infectious diseases, for example, diphtheria, scarlatina, enteric fever, variola, not only after the primary process has run its course, but even during the height or at the beginning of the disease. *A mixed infection always represents a very serious complication of plague.*

The most prominent phenomenon in the clinical picture of plague is assumed by the *enlargement of the large lymph glands in the inguinal region, axilla, popliteal space, at the elbow and in the neck.* The glandular tumors are due to the accumulation of plague bacteria, either primary or secondary, which causes an enlargement of these glands, and besides an enormous increase of the bacteria themselves, produces an edematous purulent infiltration of the glandular tissue, besides numerous hemorrhages and a transudation and infiltration of the periglandular tissue. The rapid course, causing tension of the glandular capsule, with which these processes very frequently run their course, particularly in a primarily infected gland, is the cause of the *great pain* by which the *primary buboes* are always characterized.

There can scarcely be a doubt that the infection of the primary lymph glands occurs from the lymph vessels and the infection of the lymph vessels again from the cutaneous surface. As in many diseases of the lymph glands it is rarely possible to find the primary point of entrance of the infectious product into the skin. It is a peculiarity of plague bacilli to at first cause no reaction of the tissue which they enter by means of small wounds in the skin. They are apparently carried away very rapidly from there through the lymph channels and only retained in the regional lymph glands, where they find the most favorable conditions for their development and where they have an opportunity of unfolding their pathogenic action.

In very many cases from the primary buboes, a further distribution of the infection occurs. This may be by way of the lymph tracts, in that from the primary lymph glands the *nearest regional lymph glands* are infected. But also by way of the circulation, infection of the lymph glands or of individual lymph glands at other parts of the body may arise. We may then speak of a *polyadenitis pestica* in a pathologico-anatomical sense. In this case multiple glandular enlargements occur almost simultaneously in various parts of the body, which point to a concurrent infection occurring through the agency of the blood, the blood being the common vehicle.

PATHOLOGY

There are not only clinical, but particularly pathologico-anatomical *differences between primary and secondary buboes.* It must be admitted that as well as for the clinical course, so also for the autopsy findings, this important pathologic division into primary and secondary buboes depends particularly upon *quantitative* differences. The clinician observes first one group of glands

which are enlarged and painful, and only later on, after carefully noting the progress of the disease, also finds other groups of glands that are affected, there being only, in the main, differences of intensity in the glandular tumefaction (apart from a simultaneous multiple appearance), in the intensity of the inflammation; pathologico-anatomically, there is noted but one group of glands which constantly present the signs of advanced alterations. Sero-edematous transudation, hemorrhages and necrotic process, hemorrhages into the capsule and surroundings of the gland, are mostly developed only in one group of glands, and this is the group of the primary bubo. In the secondary buboes the lesions which are characteristic of primary buboes do not attain complete development because the morbid process previously leads to death or to recovery. That, however, in fact in several secondarily infected glandular groups of the body, the same changes occur as are noted in primary bubo is proven in that these are only quantitative and not specifically qualitative differences which have led to the separation of buboes into primary and secondary.

In almost every case of bubonic plague, during the time of the chill, in the first days of the fever, upon close examination a swelling of the primary bubo may be demonstrated. Only very isolated cases are found in which, on account of marked deposits of fat, the primary seat of the plague cannot be determined. The most prominent symptom of the beginning local primary disease is the great painfulness which may often be noted in very small buboes and which may even be present before any swelling can be noted.

The majority of all buboes are found in the inguinal region. Next in frequency the axilla is affected; next the cervical buboes and following this, enlargement of the glands of the elbow. Primary disease of the glands of the neck is of special importance. Not only the proximity of the brain but above all things the vicinity of the large vessels shows these buboes to be of bad prognosis. The *tonsils* must be designated as of similar importance to the lymph glands in regard to the accumulation of the plague bacteria. *Tonsillar plague* may be readily confused with other diseases and for this reason may very easily escape a correct diagnosis.

A connection between the severity of the disease and the size of the primary bubo cannot be determined. On the contrary, it frequently appears in severe cases of bubonic plague in which an affection of the blood and many metastases rapidly occur, that only very small and painful glandular swellings exist.

As Bitter and after him Albrecht and Ghon have particularly emphasized, in the primary as well as in the secondary glandular affection there is not only one gland constantly affected; very frequently, in the majority of cases, there are groups of glands which make up the primary or secondary bubo.

The *termination of the glandular disease* may vary. In many cases during recovery, a rapid reformation of the swollen gland occurs; in other cases a softening of the primary bubo, by necrotic processes due to the influence of the toxins contained in the plague bacilli, and gangrene of the skin covering them, with rupture of the pus contained in the buboes, are noted. In some cases the great swelling only gradually lessens and only after weeks does rupture of the suppurated gland occur. Thus, frequently large pus cavities form.

The secondary glandular swellings, in general, are destroyed by absorption and necrotic processes occur less frequently in them (probably on account of a slighter number of bacilli being present), which bring about an external rupture of the gland.

Bacteriologically there are differences between primary and secondary buboes in most cases. While the primary buboes, particularly in the first stage of the disease, are uncommonly rich in the specific organism, so that the spread of a drop of the fluid obtained from a bubo upon a cover-glass and stained permits of a diagnosis, in the secondary bubo, in the majority of cases, the bacteria are less numerous and a demonstration is frequently only possible by culture or by animal experiment.

The purely etiologico-pathological conception does not comprehend the appearance of several primary effects in plague. For the involvement of several primary glands could only be explained in that at the same time, from various parts of the body, an infection with plague bacteria had occurred. On account of the circumstances by which infection with plague occurs, which may be best compared to wound infection, it is highly unlikely that such a condition may take place.

Plague bacteria have the characteristic tendency to cause *hemorrhages*, not only in the glands first affected, but also in other organs. In the animal experiment this property is also very prominent. The plague bacteria, by this biologic behavior, show their relation to the class of bacteria of hemorrhagic septikemia. Clinically, in the course of plague, it is noteworthy that hemorrhages occur in the skin, as well as in the mucous membrane of the intestinal tract. Cutaneous hemorrhages are not constant symptoms of plague. In some epidemics they occur more frequently than in others, but they are by no means a constant symptom of bubonic plague. In the epidemics of the middle ages it appears that they have been particularly frequent.

According to the views of some authors the so-called *plague carbuncles* owe their origin to cutaneous infiltrations which run their course with hemorrhages. It must be admitted that in some cases these carbuncles, also called *plague boils*, appear as a primary condition. In the majority of cases, however, they are secondary, occurring by way of metastases, through the circulation or due to stasis in the lymph channels, which terminate in necrosis and decomposition. That the plague carbuncle represents a point of entrance of the plague bacillus, the region of the first local infection, the analogue of the primary bubo must be regarded as exceptional, for in the majority of all cases of plague not the slightest change can be demonstrated in the skin. In the *majority of plague cases no inflammation of the lymph vessels can be noted*, which lead to the first diseased regional lymph gland.

The occurrence of a *primary disease of the skin*, with disease of the lymph vessels is not to be denied. Such cases have been observed, particularly in persons that have dissected plague cadavers. But in general, the appearance of small vesicles upon the skin with subsequent lymphangitis and glandular enlargement, particularly if recovery occurs rapidly, is more against a diagnosis of plague than in favor of it.

Mucous membrane hemorrhages occur in the digestive, bronchial and urethral tracts. Hemorrhagic urine is rare, intestinal hemorrhages being more

frequent. In primary plague pneumonia an admixture of blood in the sputum is a very frequent condition. But even in the absence of blood in the urine, feces or sputum, hemorrhages may occur in the tissues of the mucous membrane or in the substance of the internal organs and serous membranes.

In regard to the mode of *origin* of larger and smaller *hemorrhages* in plague, not only in the internal organs but particularly in the carbuncle process of the skin, there are two views; one regards these hemorrhages as due to the action of the toxins excreted by the plague bacillus upon the walls of the vessels in general, therefore, representing them as a distant effect, whereas the other view refers them to the accumulation of plague bacteria in the wall of the vessels, therefore, attributing them to a *local* cause. Finally, some observers wish to ascribe the appearance of larger carbuncles in plague to a mixed infection. The question regarding the occurrence of the plague carbuncle as well as of hemorrhage, in general, in plague has not yet been definitely settled; it is, therefore, advisable to await further developments before a definite and final opinion is formed.

COURSE AND TERMINATION

The symptoms on the part of the *urinary apparatus* and the *kidneys* are subordinate in the clinical picture of plague. In very isolated cases, particularly those which terminate fatally, the appearance of blood in the urine has been reported. In the majority of cases, macroscopically the urine shows no changes, and the appearance of albumin in many cases must be looked upon as a *febrile albuminuria*. Now and then a damage of the renal epithelium by the toxin of plague occurs, so that a nephritis may be spoken of, and correspondingly larger amounts of albumin and casts are found in the urine.

The *digestive apparatus* is not particularly implicated in plague, not more so than in any other severe infectious disease. Occasionally vomiting, and as the result of hemorrhages, which in severe cases takes place in the lumen of the intestine, dark-stained even bloody stools occur. The assumption of a primary intestinal plague to which individual authors have been led, by the appearance of these intestinal hemorrhages, has not been confirmed, and in general, autopsies have proved that the assumption of a primary intestinal plague in man is not justified, as it has not been possible to demonstrate a primary lesion of the intestines with primary bubo of the mesenteric glands. The demonstration of plague bacteria in the feces, by cultivation upon culture media or by a microscopical preparation, up till now, has rarely succeeded. Only in isolated cases has it been possible, by animal experiments, to demonstrate plague bacteria in the intestines, into the lumen of which they have entered from hemorrhagic mucous membrane areas. All this points to the fact, that in bubonic plague we are not dealing with a primary disease of the intestine. By this it is not meant that in very isolated cases a disease of the intestinal mucous membrane may not occur primarily. During the epidemic in Bombay, in Egypt, and in Oporto, unquestioned demonstration of the occurrence of primary intestinal plague, such as Wilm has observed in Hongkong, was not obtained.

I have already mentioned the *symptoms on the part of the nervous system*

during the acute stage. They are unquestionably due to the action of the toxins. During the period of convalescence their effect can also be noted in *trophic disturbances* and *marasmus*. The patients begin to emaciate after recovering from the disease and in many cases they succumb to progressive marasmus. Analogous symptoms are produced in animals inoculated with dead plague bacteria, and by this the above explanation of plague marasmus may be best substantiated, for it is impossible to observe in such cases that infectious processes are present in the animals.

In the complete symptomatology of plague, in all of the clinical forms, the effect upon *the heart* is most prominent. Death, which in so many cases of plague appears quite suddenly in the form of a cardiac collapse, renders it quite likely that the *toxin of plague* is primarily a *cardiac poison*. During the entire febrile period, the activity of the heart, under the influence of the toxins is quite tumultuous, and the conditions are manifold under which the action of the poison shows itself in the heart. Almost constantly, the pulse from the onset is accelerated, it may reach from 180 to 200 per minute. Hurriedly the pulse runs under the finger, sometimes with a moderate, at other times with but slight, tension of the artery. It is easily compressible and frequently shows the *symptom of the pulsus paradoxus*—as happens in a very weak power of contraction of the heart during deep inspiration (Gerhardt's explanation of the paradox pulse). In other cases the artery shows more tension. The pulse is rarely dicrotic, most frequently in the stage of onset if at all. In many instances the pulse frequency falls to 80–90 beats per minute to rise again in the next few moments to 140 and falls again in a brief period. This variation in the pulse is of particularly unfavorable prognosis. The action of the toxins of plague bacilli does not affect the heart alone, but the entire vasomotor nervous system and by this means leads to the most manifold complications, which produce the symptoms on the part of the circulatory apparatus and particularly of the heart.

Of all symptoms, those on the part of the heart are of the greatest importance in prognosis. As soon as the fever begins to decline, the pulse falls to normal; the rapidity may then decline much below the normal. This slowing of the pulse in convalescents often lasts for a long time. In many cases the effect of the toxins upon the nerves of the heart for a long time after convalescence may be noted in the conspicuous diminution of arterial tension.

Upon auscultation, weakness of the heart sounds up to complete disappearance may be noted. Occasionally murmurs are observed which are most probably functional. In the majority of cases, dilatation does not occur although Aoyama has frequently noted a distribution of cardiac dulness.

The symptoms on the part of the *respiratory apparatus* are manifold. From ancient records, and particularly from the middle ages, reports have come down to us, that plague patients frequently cough up bloody or black masses and from that time the name "black death" has come down to us. Although reports of this kind should give rise to the suspicion that in plague there is a primary affection of the lungs, to which, however, Childe was the first to bring scientific support during the epidemic in Bombay; he found that there were not only secondary foci in the lung which had already been observed by Aoyama, but that the bacillus of plague might settle primarily

in the mucous membrane of the lungs and give rise to *primary infiltration, pneumonia*. The severest cases of plague are those in which the pathogenic product settles in the lungs; the constitutional disturbances are the severest from the onset. At the beginning there is usually no expectoration and the slight coughing in many cases does not direct the attention of the observer to the fatal process, which develops in these patients. In the course of the next few days physical signs which are readily determined develop in the lungs. Râles distributed over a smaller or larger area of one or more lobes, combined with dulness in different regions, are noted. Only after the expectoration, which usually appears upon the second or third day of the disease, is examined can the diagnosis be made. Here the rational bacteriologic examination of the sputum is particularly important. An experienced observer will be able to note from a stained cover-glass preparation that he is dealing with a case of plague. For almost always in cases of primary pulmonary plague, as soon as expectoration appears, plague bacteria may be observed in great amounts and in pure culture in the more or less blood-tinged sputum. Where the microscopic cover-glass preparation is not satisfactory, culture and animal experiment will speedily make the diagnosis possible.

The course of *plague pneumonia* is usually brief and fatal. In literature some few cases of recovery from plague pneumonia have been described, but occurrences of this kind are among the greatest rarities. Almost regularly, upon the fourth, at the latest upon the fifth, day with the greatest prostration and cardiac asthenia death occurs.

From these cases of primary pest pneumonia those cases of *secondary alteration in the lungs* must be separated where in other portions of the body primary plague affections appear. We know that in a great number of bubonic plague cases, especially when an infection of the blood from the primary focus has occurred metastatic processes occur in the lungs. In such cases also a plentiful sputum may be present often showing a hemorrhagic discoloration and containing numerous plague bacilli. Metastatic pneumonias present a severe complication of plague, but they neither show the hopeless prognosis of primary pulmonary plague nor do they present the same pathologico-anatomical picture which is an absolutely different one in both forms, the primary and secondary, of plague. The metastatic pulmonary pest foci are in general pathologically in keeping with the secondary glandular swellings. While in primary plague pneumonia the infiltration is rigid with enormous fibrinous exudation and hemorrhage, the secondary plague pneumonias are characterized pathologico-anatomically by a flaccid infiltration and moderate hemorrhage.

It must be further emphasized that in many cases of bubonic plague a mild bronchitis appears and that in the secretion from the bronchi, even in milder cases of bubonic plague, plague bacteria are found. *Terminal pulmonary edema* is almost always present in fatal cases; and in the edematous fluid which ante mortem is sometimes expectorated, numerous plague bacteria are constantly found.

It need hardly be particularly emphasized that all forms of pulmonary disease in plague as regards their *contagiousness* are the most dangerous; similar to so many of the affections of the respiratory tract in which sputum

is evacuated, there is a ready opportunity for a scattering and distribution of the infectious virus with the particles of sputum which are dispersed and wafted about. Epidemiologically the pulmonary diseases have gained a particular meaning, after it has been possible to prove, *that in cured cases of pulmonary plague (secondary) virulent plague bacteria may be present in the bronchial secretion for weeks and months after recovery from the disease.*

The blood in all forms of plague may become the seat of the disease, for the *plague bacilli* may find their way to the blood from primary gland or pulmonary affections. Besides a more or less well developed leukocytosis, the plague bacilli may be demonstrated in the blood, either by a microscopic preparation, or by culture, or by animal experiment.

The appearance of plague bacteria in the blood is prognostically, naturally, a very serious omen. Although, unquestionably, cases have occurred in which recovery has taken place even after plague bacilli have been demonstrated in the blood, nevertheless in the majority of cases the demonstration of pest bacteria in the blood is a bad omen.

DIAGNOSIS

A positive and rapid diagnosis of plague is of the greatest importance as it forms the basis of international and interstate measures for combating the disease. This is only possible, and this requires to be emphasized, with the aid of a *bacteriological method of investigation*. Fortunately in the greatest majority of cases the demonstration of the specific agent is very easy. If a suspicious case occur, in which for example besides fever and marked constitutional disturbance a painful glandular enlargement appears, where it is possible to exclude venereal disease, it will frequently be easy under antiseptic precautions to puncture the bubo by means of a Pravaz syringe and then the microscopic cover-glass preparation will frequently be decisive. A drop of the fluid placed upon the cover-glass, fixed in alcohol for two minutes and stained with a watery methylene blue solution, shows in the microscopic field very frequently, besides red blood corpuscles and pus cells, large quantities of the typically formed rods. Almost always in such cases, by cultivating a few drops of the fluid upon agar and gelatin plates, and by inoculation of a few guinea-pigs and rats, it will be possible to demonstrate plague bacteria in those cases in which the microscopic cover-glass preparation does not furnish complete certainty. If the glandular swelling in diseases which are suspicious of plague is too small to permit puncture or incision, the *examination of the blood* should at once be resorted to. A drop obtained from the tip of the finger or from the lobe of the ear, under antiseptic precautions, is cultivated upon agar plates or in tubes. If this examination is conducted from one to two hours during a period of twelve to twenty-four hours, the practiced bacteriologist will almost always succeed in making a diagnosis of plague. The plague colonies cultivated from man, after twenty-four hours, have the appearance of small, dewdrop-like, transparent structures, which have a certain similarity to colonies of *R. Pfeiffer's influenza bacillus*. Besides it is advisable in such cases to obtain large amounts of blood by means of wet cups and to inoculate it into rats and guinea-pigs. In pulmonary plague the microscopic cover-glass

preparation of the sputum (assumed that this is present) is frequently demonstrative alone. Culture methods, however, in such cases, will always bring complete certainty, and animal experiments in most cases will be unnecessary. In ruptured buboes, in such cases in which the disease terminates in recovery, the demonstration of plague bacteria may be decidedly more difficult, for as experience has shown, such pus contains very few plague bacteria. Here culture methods are frequently unsuccessful and the animal experiment is necessary. Some of the suspicious pus is brought into contact with the conjunctiva of a rat, or it is applied to the shaved belly-wall of a guinea-pig, or a small quantity of the pus is injected into the subcutaneous connective tissue of rats. If plague bacteria are still present in the pus, it will be possible in many cases in this manner to demonstrate the presence of plague. A negative result of the experiment must not be utilized against the diagnosis of plague. It must still be mentioned that in doubtful cases the utilization of the terminal pulmonary edema may be of importance in the diagnosis. Hemorrhages into the skin are in general not suitable as material for investigation to determine the diagnosis.

I must briefly mention here that in the investigations at the autopsy the same view-points for gaining bacteriological material of investigation are determining as in the living subject, and that in true cases of plague which soon after death come to autopsy it will almost always be possible to demonstrate plague bacteria. In combating plague in the Orient the investigation of the cadaver plays a particularly important rôle, more so than is generally assumed, because on account of religious and fanatical reasons the Orientals in India, Arabia and Egypt so frequently attempt to conceal the disease from the authorities.

I must still mention *serum diagnosis* in plague, a method of investigation which is also of importance in enteric fever. As is well known, not only after infectious diseases have run their course but even during their existence, occasionally, for example, in enteric fever, quite early specific changes occur in the blood which, on account of their behavior toward the specific pathogenic agents, either in the test tube or in the animal organism, are capable of being demonstrated. Minute study of these products has shown that we have to deal with two groups of substances, which during, or in the course of, an infectious disease make their appearance, namely, the *bacteriolitic* and the *agglutinating* products. Independently of each other both may be present, or only one of them may appear. In human plague, toward the end of the disease and in convalescence, in a certain percentage of cases the *agglutinating properties* of the blood serum appear. If a small quantity of the serum of such a patient is taken and then placed in culture-media after it has been diluted in a physiological salt solution in the proportion of 1 to 3, admixed with plague bacteria, there occurs in contrast to normal serum, which does not influence plague bacteria even undiluted, *an agglutination of the bacteria into small clumps*. Small flocculi appear in the mixture, which in the course of the next half an hour to an hour become larger; these sink after some time, leaving the fluid above completely clear in an identical manner as occurs in the well known reaction in enteric fever. *It is of great importance to note that this phenomenon does not occur in by far the greatest number of cases*

of plague. It must therefore be emphasized at the start that a negative result of the agglutination test in plague proves nothing against the presence or recovery from plague.

A positive result of the agglutination test in combination with the determination of previous clinical symptoms may be utilized in the diagnosis of plague. Although this has little clinical importance such a determination under some circumstances may be of great prophylactic and epidemiologic importance.

I must still mention that also in the serum of animals which have been immunized with plague bacteria these specific products may appear and that the utilization of such substances in the identification of a suspicious bacterial culture, as a plague culture, has been advised by various authors.

PROGNOSIS

Regarding the prognosis of plague, this is naturally always serious in an affection in which about 50 per cent. of all cases terminate fatally and which runs so rapid a course. Although in many cases the prognosis is indefinite, in other cases we have certain points of support such as I have already mentioned for judging the severity of the case, particularly in the direction of an unfavorable prognosis. The seat of the bubo in the neck, an early appearance of plague bacteria in the blood, primary plague pneumonia, very early severe constitutional symptoms with slight development of the primary bubo, according to our present experiences make it extremely unlikely that recovery will occur. The other symptoms including the fever have no great prognostic importance. Frequently in cases in which all signs point to a favorable issue, death occurs quite suddenly, due to paralysis of the heart. The heart in general is of primary importance in our consideration as soon as we are investigating the general symptoms and effect of the infection upon the body, and the physician will be best able to determine the course of the disease from the condition of the heart and the pulse.

Naturally also symptoms on the part of the nervous system, as well as those on the gastro-intestinal tract and their intensity, as in all infectious diseases, play a certain rôle in determining the question, whether it will be possible for the body, with its natural powers of resistance, to obtain a victory against the infecting bacteria. Age, sex, race, climate, social condition do not appear to have a great influence upon the mortality and it is therefore scarcely possible to draw prognostic conclusions from them.

TREATMENT

The therapy of plague, particularly in ancient times, has employed all remedies known to the *materia medica*, but, as is well known, up to the present day neither an internal nor a surgical treatment of plague has been successful. In India and in other regions, where plague has shown itself in the past century, the impotence of medicine has been demonstrated in gaining the victory over this dreadful disease. In bubonic plague, when suppuration has occurred in the glands and they are near to rupturing, surgical precepts for opening the necrotic gland masses are to be followed and there are also

surgical measures which have for their purpose the prevention of possible secondary infection with pus bacteria, by antiseptic washings and appliances. In the main, however, the extirpation of the glands has not been particularly successful, so that in bubonic plague as well as in pulmonary plague we are even to-day forced to adopt an internal form of treatment. Naturally the physician dare not neglect, in such cases, to carefully individualize and to combat at least certain threatening symptoms. In this respect, primarily the heart is to be considered; its activity must be watched and stimulants, above all alcohol, must be used with the hope of maintaining its force. It is true, during the epidemic in Bombay, of the many remedies which have an effect upon the heart, and were plentifully used, an unquestioned life-saving effect, in threatened cardiac collapse, has been rarely noted. Other methods of treatment, as, for example, hydrotherapy, have not shown results up to this time.

Nutrition scarcely requires special mention. The general methods adopted in the treatment of fever patients are the ones to be used here. Suitable nutrition, as occurs for example in enteric fever, the administration of tonics and wine, is probably the best method.

For a time it appeared as if a *plague serum* which was first proposed by Yersin, according to the principles of serum therapy, would be successful. Yersin and Roux in their experiments proceeded in the following manner: They utilized larger animals, particularly horses, immunizing them first with dead bacilli, plague cultures grown in bouillon, and then later with increasing doses of living virulent plague cultures which were intravenously injected. The serum of such highly immunized horses, according to Ehrlich's principles, was said not only in the animal experiment to produce a protective and curative action, but also to be effective in the human plague patient. That a serum of this kind should have a protective as well as a curative action in the animal experiments has been demonstrated in numerous trials in animals, but even in a simultaneous infection and serum injection in highly susceptible animals, for example monkeys and guinea-pigs, the success of serum injection is frequently problematic. Unfortunately the experiences which have been gathered in human beings with the plague serum have not been capable of demonstrating convincing proofs for the activity of the plague serum, that is to bring about the recovery of the plague patient. There are statistics by various authors and particularly by Yersin, which have been published, which make it appear as though the plague serum in fact produced favorable action upon the course of the disease, but such statistics frequently are not convincing, for cases of the same gravity have not been treated. The course has been usually such that patients have been *selected* in hospitals for serum treatment. The only correct method of deciding the activity of the plague serum would be, that every patient brought into the hospital, without regard to the severity of the disease, should be at once injected with plague serum upon admission to the hospital. In this manner, in large epidemics, an opinion regarding the activity of the plague serum could certainly be gained. Such an attempt would be of great scientific interest and value. Such statistics, however, do not exist and in the few cases in which good results have been reported others have been opposed to them, in which abso-

lutely no influence upon the mortality during different epidemics has been determined. It may still be mentioned that upon the basis of animal experiments antitoxic properties of the serum have not been determined, but only the so-called bacteriolitic products of R. Pfeiffer.

In how far the plague serum, which certainly possesses a specific activity, is to be considered for purposes of *passive immunization* (analogous to the passive immunization with diphtheria serum in the relatives of a diphtheria patient) very few reports are at hand, as very few inoculations have so far been attempted. But even if such protective inoculations were effective they would only convey a transitory protection and could only be employed in connection with other prophylactic measures. Numerous experiences have, however, shown that with our ordinary prophylactic measures it is very frequently possible to prevent the distribution of a plague epidemic, for example, upon ships and the like.

Persons who have recovered from plague, according to the unanimous report of most observers, are very rarely attacked a second time. It appears, therefore, as if a single recovery from plague conveyed a lifelong *immunity*. It is true cases have been observed in which by bacteriological, clinical and anatomical investigation, after recovery from an attack of plague, a relapse has been observed. Griesinger has reported, that in individual cases, one and the same individual was attacked by true plague, twice during the same epidemic. These facts, which may be looked upon as certain, do not contradict the fundamental rule that a single recovery from plague conveys a comparatively powerful immunity. We also know that in measles, which most human beings have but a single time, which, therefore, by a single recovery from the disease conveys an immunity which lasts for life, cases are noted in which persons twice, even three times, in brief intervals are attacked with measles. Biologic laws do not reveal the rigid forms such as we are accustomed to observe in physical phenomena. There are transitions and exceptions in these biologic processes, and even in plague there may be individual differences in the degree of acquired immunity in different human beings. Not absolute, life-long, but relative and a timely limited immunity may be acquired by recovery from plague, similar to the case in ordinary vaccination.

The measures which have led to the application of protective inoculations in plague are based upon the observation that a *single recovery from plague conveys a marked protection*. These protective inoculations have been practised particularly in human beings by Haffkine to a great extent in India. They are similar to those protective inoculations which Haffkine practised in the same country against cholera. The experimental points of support for these trials have been gained by the labors of a number of investigators, particularly in cholera and enteric fever (above all R. Pfeiffer and W. Kolle) by which it was shown that it is possible, particularly in guinea-pigs, to protect them against infection by dead cultures of typhoid and cholera cultures. While in cholera and enteric fever these animal experiments have led to a comparatively uniform result, showing that a single injection of a larger amount of dead cholera or typhoid cultures protects the animals against infection with certainty, with a minimal lethal dose, the results in plague, even in the animal experiment, are not so successful and hopeful. The

German Plague Commission, for example, was able to determine that a single injection made even from a dead plague agar culture, was not able to protect a rat with certainty against infection by way of the mucous membrane, a mode of infection which is particularly frequent under natural conditions. These animal trials, which were but little encouraging, were later carried out in greater extent.

A *virus* for inoculation that is to have practical importance must answer three conditions. It must be absolutely harmless, therefore free from living plague bacteria; it must act with certainty and finally must not produce too great constitutional difficulties in the inoculated person. Haffkine utilized bouillon cultures of dead plague bacilli, which he cultivated for four weeks in vessels holding 2 litres. There then develops upon the surface of such vessels a membrane which consists of plague bacteria, sinking from time to time and replaced by a new one as the result of surface growth, which is favored by the addition of the fat of butter to the bouillon.

These cultures, after a month, are tested by culture regarding their purity, then the fluid is distributed in different test tubes and sterilized by heating for one hour at a temperature of 70° C. With this process the inoculation product is finished. Before it is injected carbolic acid is added. The dose at the beginning was mentioned as from 2 to 3 cc. Later Haffkine found it necessary to increase this dose to 15 and even 20 cc. The German Plague Commission, which based its experiments on protective inoculation in enteric fever and plague, and the experiences gained in animal experiments, utilized agar cultures twenty-four hours old. The top of the culture is scraped off, placed in bouillon and heated for an hour at 70° C. Before using carbolic acid is also added. The latter process is to be decidedly preferred, not only because the dosage is more uniform but because the premises under which Haffkine manufactured his inoculation virus have not been realized. For the assumption that, in old bouillon cultures, toxic products of metabolism of the bacteria appear, which possess special immunizing properties, could not be verified in testing the culture filtrate. The investigations of the German Plague Commission have shown with certainty that particularly the use of fresh, highly virulent cultures produces particularly energetic protective action, and in the Haffkine process the virulence of the culture declines, as he admits himself, during the long presence in the incubation closet.

It is immaterial whether the inoculation products obtained from bouillon cultures or from agar cultures are used for injection, the reaction in man in the main is the same. A painful infiltration in the surroundings of the point of inoculation appears which only disappears after several days. Occasionally the regional lymph glands are painful and enlarged. A few hours after the injection a rise in temperature to 100.4° F., even 102.2° F., may occur, which, however, in the course of a few days again falls to normal. Among constitutional symptoms there are headache, lassitude and absence of appetite. From conclusions of analogy in the immunizing experiments in animals with typhoid and cholera we will not go far wrong if we assume that the inoculation protection in man, who is so actively immunized, does not occur before the fifth day after the injection, and only upon the tenth day after the injection is this complete.

Regarding the duration of the immunity attained by inoculation nothing definite can be said, but many observations favor the fact that it is hardly one of long duration and certainly does not go beyond one year. In judging the results of the protective inoculations in India, particularly advised and carried out by Haffkine, statistics must be depended upon. We are indebted particularly to the Egyptian Plague Commission, above all to Bitter, then also to a Commission which was sent from England under Wright in 1898-99 to India, for more accurate views regarding this important question. They determined that the statistics published by Haffkine showed quite important sources of error. In many cases the proof was brought that the persons who subjected themselves to inoculation were exposed to infection later on in a quite different manner. Nowhere do the conditions of life under which the inoculated persons lived, whether they belonged to the well-to-do or to the poorer classes, whether to the upper castes, the Parsees, or the lowest caste, nowhere do these conditions play so great a part as in plague. Upon closer observation the majority of the favorable results which Haffkine claims to have attained were shown in a less favorable light. Always in individual outbreaks of plague, in districts in which protective inoculations were the prominent protective measures, a certain effect could be determined, namely, regarding the influence which these inoculations showed upon the course of an affection which occurred at a later period.

Under these circumstances it is not advisable to use an obligatory method of protective inoculation and without selection, one which has been so little used, when a strict prophylaxis, which may be rapidly carried out, would much sooner serve the purpose of stamping out plague. The difficulty also of carrying out such protective inoculation methods in a large number of persons is so great that the hygienic and sanitary measures in general, even to-day, are still most prominent. Under certain conditions, it is true, it will be advisable to actively immunize some persons who are particularly exposed to infection such as physicians, nurses, the inhabitants of ships upon which plague cases occur.

EPIDEMIOLOGY

In reviewing the newly gained facts regarding the epidemiology of plague we must admit that there are still many points which have not been cleared up in spite of the endeavors to throw light upon the subject regarding the development and distribution of plague epidemics in individual regions, but the application of bacteriological investigation even in this direction has given us an insight in this respect.

At the present time four endemic foci are assumed, from which plague distributes itself from time to time in epidemics. One of these is found in China in the Province of Yunnan, a focus with which the outbreak of plague in Hongkong is unquestionably in connection. A second area is situated in the Himalayas from which the Bombay epidemic may have found its starting point. R. Koch succeeded in 1898 in demonstrating a third focus in Uganda and finally different outbreaks of plague point to Southern Russia, a fourth focus in the Caucasus. If from these ends of the world in which plague is so firmly entrenched, the disease appears in the great highways,

then in general it increases in its distribution with great rapidity. The plague epidemics of antiquity traversed the entire known world at that time and the epidemic of "black death" is said to have sacrificed about 25,000,000 persons in Europe alone. If to-day when travel is so immensely increased compared with the times of the middle ages the number of victims of the plague, in spite of its occurrence in various parts of the world, is so much smaller, it may be concluded from this alone that the conception which we have obtained regarding the distribution of the plague is in general probably correct, and this has been of apparent influence also in regard to preventing its distribution.

In a very prominent manner and perhaps much more conspicuously than cholera, plague shows itself as a disease which has a preference for seaports. We note if we follow the outbreaks of the last five years, that everywhere it gained its first footing in seaport towns when the disease invaded a new continent or a new country. In contrast to cholera, plague shows a tendency to intrench itself gradually and frequently unobserved, but when it has once gained a footing it can only be stamped out with the greatest difficulty. A striking example of this is furnished by Bombay, where plague for four years, after it had distributed itself among the poorer population in an unknown manner, gained such a footing that up till now it has not been possible to stamp out the disease.

A dependence of the distribution of plague epidemics upon climate and temperature in general could not be determined. Moist and low temperatures favor the distribution of the disease more than a hot and uniformly dry climate. Although the tendency of plague to follow the great roads of commerce and travel naturally increases the danger of trans-oceanic communication, this circumstance particularly shows a method of preventing the distribution of plague and to early isolate it.

Man is naturally most in danger of contagion. Transmission from man to man may occur directly or indirectly. The secretions of the respiratory tract are most dangerous which are strongly permeated with bacilli, above all other forms in pulmonary plague. Contagion from these cases may occur either by the inhalation of dried sputum or by the rubbing of sputum into the skin. If we designate the skin and external mucous membranes, on the one hand, and the lungs (tonsils) upon the other, as points of entrance, it has not been possible to show that the intestinal tract is a point of entrance for the disease. For this reason water cannot play a part in the distribution of plague and by no one has such a rôle been assigned to water up to now.

Of especial importance, in the same manner as in cholera, are the cases which terminate in recovery; the disease is often distributed from ruptured buboes, which are healing, as well as from the secretion of the same, and in the bronchial secretion bacteria are contained which remain active for a long time and are thus capable of producing infection. Thus it may be seen how readily, in this manner, a distribution of plague may occur quite apart from the fact that in mild, unrecognized plague cases also the belongings of the patients, such as clothing, etc., are infected and therefore capable of distributing the infection. The same is true of the mild and mildest plague cases, as such

patients that have buboes which may scarcely be observed frequently follow their occupations, may walk great distances, or are able to travel without appearing to themselves or to those who surround them as ill, and still the mildest cases of *pestis ambulans* are occasionally infectious! How difficult the epidemiologic connection, the thread from one morbid focus to another, will occasionally be to determine, need hardly be mentioned, as the same conditions have been so frequently noted during the last epidemic of cholera in Germany.

The circumstance that besides man animals also suffer from plague makes the epidemiologic investigation of plague very difficult, and this is an important factor for the conception regarding the distribution of plague epidemics. *Plague epizootics* may occur among rats as well as mice. The observation of former epidemics shows that the outbreak of plague was preceded by an enormous death rate among rats and mice. During the plague outbreak in 1894 a great mortality among rats was noted, at the same time or after the outbreak of plague among human beings. It is, however, especially important that various investigators have succeeded in demonstrating in rats, which were found dead during a plague epidemic and which were examined, plague bacteria and the changes typical of plague. Although the last word has not been said as to whether or not rats are chiefly responsible for the appearance of a plague epidemic, and although the views, whether rats play a most important rôle in the distribution of human plague or not are still wide apart, this much may be looked upon as certain, that in many cases there is a connection between the distribution of human plague and rat plague epizootic.

Insects do not appear to play an important rôle either in the distribution of plague among human beings or among animals. In rats, in most cases, the infection is produced by gnawing animals which have succumbed to plague. In many cases in which dead rats have been examined, the primary buboes were found in the region of the lower jaw, a point of support for the opinion that the port of entrance was in the mucous membrane of the mouth or of the nose. The transference of plague from rats or human beings to man by fleas has not been proven with certainty, although it must be theoretically admitted that this may occur and occasionally has now and then happened. As an important epidemiologic factor, however, this is not to be considered.

In 1896 after the plague had attained decided distribution in Bombay more energetic prophylactic measures were adopted, unfortunately not with very great success. It was shown here that particularly under the difficult conditions with which one had to reckon in India, on account of religious and other circumstances, there was slight hope of mastering the plague after the disease had fully intrenched itself in a city. The observation was made, particularly in Bombay, that in some houses and in some streets repeatedly in spite of disinfection and removal of the sick, new cases of plague occurred. There were *plague houses* and *plague quarters*, and only by destroying such houses by fire was it possible to stamp out the individual foci.

These observations also led European countries to adopt prophylactic measures to prevent the introduction of plague. At the *International Sanitary Conference* at Venice in 1897, which was called by Austria, certain quar-

antine rules were adopted, looking toward the prevention of the introduction of plague by way of the sea. It was attempted there, above all things, to carry out certain measures to keep the plague confined to its point of outbreak in India and prevent its entrance into Europe. Thus, for instance, Russia attempted, by placing a military cordon, to prevent the plague from coming in by way of Asia Minor and the Caucasus. It is obvious that protective measures of this kind are not likely to check a pestilence which almost has the power of a natural element. More may be hoped from the measures which were adopted by the Sanitary Conference for the pilgrim ships and for the ships going from India to Egypt. It was determined that the water route through the Red Sea and the Suez Canal should be controlled in such a manner that ships which had left an infected harbor at least ten days previously, provided they had no case of plague on board, might pass the Canal in quarantine, that is, they were not allowed to hold any communication with the land. The ships which had plague on board, the patients, however, having recovered at least twelve days before the arrival of the ship, were characterized as suspicious. If such ships had a physician and a disinfecting apparatus on board they were allowed to pass the Canal in quarantine; if not, they were detained for examination of the passengers and for disinfection of their belongings. If a ship in the last twelve days before landing had cases of plague on board, or if there were still plague cases on board, the ship was required to enter the sanitary station at the Moses Springs. There all passengers were landed, the patients were isolated, placed in small booths and guarded for ten days; the entire ship and everything on board was disinfected.

Besides, special regulations were adopted for the pilgrims, the Moham-medans going to Mecca from Europe, North Africa and India. It was stated how much space, what amount of food and water was to be allotted to every pilgrim. There was also to be a hospital and a physician on every ship. For neglect of these regulations the captain of the ship was to be punished. Upon returning, the pilgrims were to be examined upon the peninsula Sinai in El-Tor; the pilgrims coming from India were to be examined in Jeddah, the harbor of Mecca and eventually sent back.

The Venetian Conference allowed the individual States to combat the plague in their own countries, but each State was obliged to inform the others by means of diplomacy of cases of plague (determined by bacteriology) and to furnish weekly reports as to the course of the affection. If in a district a case of plague had appeared it was to be regarded as infected until after the house had been disinfected, etc., and ten days had passed without another case arising. There was to be no quarantine in rural districts, patients were to be detained at the border line and all travelling companions examined by physicians. Ships coming from infected ports, or upon which a plague patient had been ten days previously, were compelled to serve a quarantine lasting ten days. If cases of plague had occurred upon a ship, the belongings of the passengers, as well as the ship, were cleansed and disinfected, particularly the sick rooms and the steerage way.

Although *protective measures of this kind* certainly *diminish the danger* of importing plague, it is nevertheless clear that they do not absolutely prevent the entrance of plague to Europe, as witnessed by the occurrence of the

disease in Oporto, Triest, Glasgow, Hamburg and Bremerhaven. No illusions should be allowed to prevail regarding the efficiency of shipping control.

From what has been said above, regarding the infectiousness of mild cases, i. e., those cases in which plague appears in a mild form without being recognized as such and terminates in recovery, as well as the circumstance that rats and mice are present upon every ship and are thus exposed to the contagion, it follows that even if all regulations in respect to disinfection and quarantine were observed, the introduction of plague, under some circumstances, in spite of all care, could not be prevented. But even if a few cases should gain access to a port of Europe or America there are certain measures which have shown themselves effective which were based upon our experiences with cholera.

In a similar manner, as in the prophylaxis of cholera, inaugurated by R. Koch, the foundation of plague prophylaxis depends upon a positive and rapid diagnosis of the disease. Although the clinical symptoms, in a typical case permit us to make the diagnosis, yet to eliminate all doubt, in one or the other direction in suspicious cases, a bacteriological examination is necessary. I need not call attention to the fact that in the diagnosis of the first case special care is to be exercised, as diplomatic and commercial consequences depend upon the recognition of plague, upon the basis of the Venetian International Conference. In Prussia, as well as in various other countries of Europe, not only have plague laboratories been erected in which proper measures are operative to prevent the further dissemination of the plague and for the purpose of arriving at a rapid diagnosis, but a great number of physicians in Germany have been especially educated for the duty of making the correct diagnosis in case of doubt. Portable laboratories are constantly at the service of such physicians, which are sent from place to place. Special credit for carrying out these, as well as many other measures in connection with State Medicine in Prussia, is due to Prof. Kirchner. A new law in Germany compels notification followed by inquest in fatal cases of all suspicious plague patients; this being a decided step forward in the prophylaxis of these exotic diseases. In the main, isolation of plague cases in suitable barracks, disinfection of the effects and of the dwelling places of the patients, observation of those who have come in contact with the sick for a long period (eventually protective inoculation) are the proper prophylactic measures. All attempts to exterminate rats during times free from plague have been unsuccessful so far. Neither chemical agents nor pathogenic bacteria of other varieties have been capable of rooting out these vermin. It would certainly be a step in advance if success should crown our efforts in the future, if only to obtain a correct view regarding the significance of rats in the distribution of plague.

An attempt has been made several times, within the last few years, in Egypt. There, in former epidemics, from the time of the Pharaohs up to the middle of the last century, the plague has always been widely distributed as soon as it was introduced from the Orient, usually from Asia. Only after years of dominance of the pestilence and great decimation of the population would the disease disappear from the valley of the Nile. When the last Bombay epidemic threatened to invade Egypt, the Government organized a pro-

tective system under the direction of Bitter, Pinching-Bey in Cairo, Schiess-Bey and Gotschlich in Alexandria, according to the principles mentioned above, which were so effective in combating cholera in Alexandria, Port Said and in other districts. And although plague gained a footing in some harbor cities, such as Port Said and Alexandria, the protective measures, indicated above, were always successful in suppressing the disease and stamping it out in a few months. Even, therefore, if rats play a part in the distribution of plague epidemics the success of hygienic measures in Egypt indicates that even without exterminating rats, plague may be stamped out if we are energetic and quick enough with our prophylaxis.

I will conclude this article with a remark, which though retrospective, opens up a pleasing prospect for the future. The labors of investigators have contributed much in clearing the situation regarding the etiology and nature of plague. The past century was successful in discovering the cause of many of the great pestilences and no less so in advancing positive prophylactic measures. Entering upon the threshold of the new century we may hope that, particularly in the case of plague, in which research has been so successful in the last decades, the further development of experimental therapy based upon etiologic and biologic investigations in immunity may furnish us with the specific remedy in the course of the twentieth century. That which has been accomplished in prophylaxis may be regarded with justifiable pride.

[See also Serum Therapy, page 909.]

EPIDEMIC PAROTITIS, MUMPS

By H. FALKENHEIM, KÖNIGSBERG

CASE HISTORY.—A boy aged seven, entirely well up to a short time ago. Since three days ago not as active as previously. He began to show pallor, lassitude, he became irritable without definite symptoms of disease making their appearance. The mother then consulted a physician, as the child was very restless the night previously, complaining of earache and because a swelling had appeared upon the left half of the face accompanied by fever.

The swelling is quite conspicuous. It occupies the region in front of the ear, reaches from the zygomatic arch downward to the angle of the jaw and reaches the posterior margin of the branch of the lower jaw to the groove between it and the mastoid process of the temporal bone, forcing the lower half of the ear, particularly the lobe of the ear, outward and somewhat anteriorly. The skin over the swelling appears pale, glistening and tense. The tumor itself has an elastic feel and is somewhat painful upon pressure. The child is hindered in eating, as pains arise in chewing. The tongue is coated, oral mucous membranes slightly reddened. The temperature is somewhat raised, 101.3° F. No other symptoms are discernible in the boy.

The mother declares, upon being asked, that similar cases had not occurred in the child's brothers or sisters, but a playmate of the patient was affected in a similar manner fourteen days previously.

The diagnosis is made by the mother. The boy has mumps, a condition which naturally will get well, but a school certificate is necessary, as the boy in his present condition is not permitted to go to school.

In fact there is a swelling of the parotid gland. The gland is affected in its entirety. In a characteristic manner the swelling produces an alteration in position of the lobe of the ear. The limits of the enlarged gland may be readily determined by palpation. The swelling produces a doughy sensation in the surrounding areas. The nature of the glandular swelling, the absence of inflammatory changes upon the skin which covers it, the previous history, with the report of a similar affection in a playmate, the absence of other symptoms which might produce a swelling of the parotid, make it appear that the diagnosis of the mother is correct. The disease is well known among the laity on account of the peculiar distortion produced by the glandular swelling and the condition becomes particularly noticeable in bilateral disease, the patient assuming a stupid, ludicrous appearance which has led to the disease receiving a number of popular names. It is well known that the disease in the main has a favorable prognosis and in a great majority of the cases does not require treatment.

The patient whose history was just quoted showed a very mild affection, but on account of the fever rest in bed was ordered; to allay the tension of the gland, inunctions of warm oil covered with cotton, and a mild antiseptic mouth wash were ordered to keep the oral cavity clean; a bland fluid diet and a laxative were further administered. No complications having arisen and in particular, as is so frequent, the other side not being affected, the patient was completely well in a few days.

HISTORY AND ETIOLOGY

The knowledge of parotitis epidemica reaches far back. Hippocrates has given an accurate description of the disease. His experiences completely coincide with ours to-day. The benign character of the disease, the predis-

position of youthful individuals, the extraordinary rarity of suppuration of the gland, the secondary inflammation of the testicle, were all known to him. The disease has not changed its character for centuries. It does not appear to be limited to particular climatic conditions. It has been noted in all zones and in all seasons. In the temperate zone it appears that the colder season seems to favor the disease. Thus in 117 epidemics collected by Hirsch, 51 occurred in winter, and among 99 collected by Leichtenstern which were accurately studied, 42 began in the first quarter of the year, 17 in the second, 9 in the third and 31 in the fourth. Prolonged cold and wet weather, sudden appearance of a cold season seem to favor the development of the affection.

The contagiousness of mumps is beyond all doubt. As observations have taught us, transmission of the disease may not only occur at the acme of the infection but even before the glandular enlargement has appeared, and on the other hand contagion may even occur in convalescence. As a rule, contagion occurs directly from person to person, but the disease may also apparently be conveyed by a third person, even by fomites.

The extension of the disease occurs quite gradually. The contagium distributes itself but slowly and only for short distances. Thus in boarding-schools, at first the inmates of the beds nearest the patient are attacked by the disease and then the disease is arrested, but this may occur, on the other hand, as the result of simple isolation. Often the disease only occurs in a single building, a school, an orphan asylum, a prison, a fortress, and does not occur beyond the walls, disappearing after all predisposed inmates have had the affection without attacking those living beyond these confines. At other times a house epidemic becomes a city epidemic or even affects an entire province. The disease may even obtain pandemic distribution. As in the case of scarlatina, measles, sporadic cases also occur in parotitis epidemica. In some regions mumps appears every year, in other districts only every five or every ten years, again sparing other regions for a much longer period. There are no distinct relations to other infectious diseases, such as to scarlatina or measles, etc. The epidemics may occur in different groups and occur side by side. That children attacked by mumps are not affected by scarlatina, as was observed by Schönlein and Frank, has not been confirmed by later observers. The simultaneous occurrence of mumps with measles, with vari-cella, with influenza, was noted by Hochsinger a few years ago (*Centralbl. f. Kinderhk.*, 1898, Nr. 12).

The infectiousness varies in different epidemics. While in one the majority of children are attacked, especially if they come in closer contact with each other, thus, for example, in an orphan asylum in Moscow among 300 children, 167 were attacked; in an epidemic observed by Lühe in a cadet school in Ploen, among 131, 118 were attacked—in other epidemics, in families, in children's hospitals, without special isolation, but few cases have occurred, although the inmates had not previously suffered from the disease. The severity of the affection in different epidemics is also subject to certain variations. In some, though comparatively rare, the cases lose their harmless, ludicrous character, a severe disease appearing with threatening complications.

As a rule, the disease attacks an individual but once, second attacks being exceptional. More frequent attacks than this are extraordinarily rare, par-

ticularly in children. Comby saw a girl aged twelve years have an attack of mumps three years after a first attack. Both attacks were unmistakable. Soltmann has seen several such cases and Hochsinger only recently reported cases of this kind.

Children between the ages of five and fifteen are especially liable. Children under two and the aged are rarely attacked. In adolescence the predisposition is still quite marked. There are numerous reports, especially from France, regarding epidemics occurring in barracks. After the fortieth year of life the disease is very rare. The greater predisposition of youthful age, as Leichtenstern remarks, may also be distinctly seen from the fact that in a house epidemic first the younger children then the older ones and finally, if at all, the adults are attacked. In 73 cases Rilliet and Lombard noted the affection in 37 children between five and fifteen years, in 7 between three and four years and none at an earlier age. Soltmann's youngest patient was a year and three quarters old. Steiner's, one and a quarter year old. My youngest patient was only seven months old. It is entirely exceptional that children as young as this are attacked. As a rule nurslings and the newborn are immune to the disease and repeatedly a wet nurse who has been attacked by mumps has been allowed to go on nursing the child, without the child having been attacked by the disease. Gautier observed in an infant, whose mother was attacked by mumps, a swelling of the submaxillary gland. White saw a child six days old and its mother a day later, attacked by parotitis, the mother having a severe affection, while other cases occurred in the neighborhood simultaneously. Homans found, in the child of a woman whose labor came on in the eighth month as the result of parotitis, a swelling of the left parotid gland on the day after birth. The swelling increased upon the two next days and was distinctly painful. These observations permit us to reflect upon the possibility of intrauterine transmission.

Sex does not show a difference in regard to the disease. The apparent predominance of the male sex is due to the greater frequency with which this sex is exposed to contagion, as in schools, cadet schools, barracks, etc. (Comby).

The infection in all probability occurs from the oral cavity and the germs find their way thence to the mouth of the glands. On account of the lack of development of these glands and on account of the narrowness of Steno's duct in nurslings, Soltmann sees the condition which confers immunity at this age of life. Many attempts have been made to discover the nature of the pathogenic agent. Up to the present no uniform result has been obtained. The investigations of Laveran and Catrin deserve attention, these authors detected in the blood, in the parotid and in the testicle, in the fluid of the edema, diplococci. The investigations of Michaelis and Bein, who in two cases found diplococci in Steno's duct and in the pus of an abscess of the parotid are also noteworthy. These investigations, however, require further proof.

PATHOLOGY

What *pathological changes* occur in the parotid in mumps have not been determined with certainty. Pure cases are not fatal. As only changes can occur which are susceptible of complete cure it is assumed by analogy that

a sero-fibrinous transudation of the periglandular and inter-acinus cellular tissue occurs, whereas the tissue of the gland itself in the main presents a normal condition. Gerhardt saw the diseased gland furnish a secretion which corresponded to the normal. Lombard noted the same condition. Jacob found, in a soldier who was attacked by mumps and who perished on account of edema of the glottis, that the salivary gland was not enlarged, but the cell stratum was filled with a greenish gelatinous fluid, the entire tissue being of a lardaceous consistence. Ranvier proved the absence of inflammatory changes by microscopic investigation. The epithelium of the glandular canal was unchanged, cell proliferation was not present. There was edema of the glottis, edema of the inter-acinous tissue. That, however, in severe cases the gland cells may also show anatomical changes is quite possible. Suppuration occurs exceedingly rarely in parotitis; and then only a part of the gland is destroyed. Although in a portion of the cases the assumption of Leichtenstern may be true, that areas of the gland, as the result of high grade of swelling, are disturbed in their nutrition and thus destroyed and desquamated by demarcation, in other cases there is only a secondary infection with pyogenic agents from the mouth.

After infection has taken place a *period of incubation* arises, the duration of which has been variously estimated by different authors. In general we may count eighteen days, although somewhat longer periods of incubation (twenty to twenty-two days) are also quite frequent. Demme saw several cases in which the period of incubation lasted but three days. Dukes noted cases in which this was twenty-four days.

SYMPTOMS

Prodromal symptoms vary in individual epidemics. They may be entirely absent in a number of cases or so slight that they are overlooked and only the swelling of the gland denotes the presence of a disease. In other cases the children become irritable, unwilling to play and are languid. They lose their appetite, their sleep is disturbed, fever occurs, which exceptionally may reach even 104° F. Older children even complain of headache, of fleeting pains in the parotid region, the sensation of a certain tension in the neighborhood of the angle of the jaw upon opening the mouth. The mucous membrane of the mouth shows catarrhal inflammation. Younger children grasp their head and the ear with their hands. The gastro-intestinal symptoms are quite marked in some epidemics. Soltmann in his youngest patient saw the attack begin with severe fever and an eclamptic attack. Rarely do these prodromes last longer than from one to three days; then with increasing sensitiveness in the parotid, with an increase in tension, with a growing limitation of the movement of the jaw, the swelling in the parotid rapidly appears, most often upon the left side. The gland rises in the groove between the lower jaw and the mastoid process, shows itself as a broad swelling, transversely over the branch of the inferior maxillary and distributes itself in the region in front of the ear. The lower portion of the ear is raised, forced somewhat anteriorly and the readily movable lobe of the ear is almost placed in a horizontal position. In intense cases the swelling advances beyond the immediate surround-

ings of the parotid. The subcutaneous cellular tissue becomes edematous, infiltrated and has a doughy feeling. The limits of the parotid become indistinct, the swelling in some cases may reach to the orbit, the palpebral space becomes narrowed, the conjunctiva injected. The swelling may distribute itself over the entire cheek up to the angle of the jaw and the submaxillary and sublingual glands may take part in the morbid process, the swelling reaching to the clavicle. The normal division of the neck is then lost, the region of the neck is broadened, and if the disease occurs bilaterally the neck may be broader than the face. Occasionally the parotid as a whole is not attacked at once, but in individual exacerbations. The skin over the swollen area is tense, pale, glistening. The glands are sensitive to pressure. It is noteworthy that in some cases the submaxillary gland, more rarely the sublingual gland, are alone attacked (Penzoldt), whereas the parotid may be spared or only be affected later on (v. Strümpell). These cases gain a certain diagnostic interest, particularly when judging of secondary clinical symptoms after the swelling has disappeared. Under some circumstances in a family one child may be seen with a swelling of the parotid, another child with a swelling of the submaxillary gland.

By means of the enlargement of that portion of the parotid which rests upon the biventer in the retro-maxillary groove, such pressure may be exerted that the resistance of the deep fascia of the neck may be overcome. The lateral wall of the pharynx with the tonsil will then be forced anteriorly and the isthmus of the fauces narrowed. Pressure may be exerted upon the larynx and upon the upper portion of the trachea. Partly as the result of pressure upon the vessels, edematous swelling of the mucous membranes of the pharynx and of the larynx may occur, as also the symptoms of severe laryngeal stenosis. On account of disturbance in respiration in connection with venous hyperemia as the result of pressure upon the veins of the neck, in bilateral, high-graded parotitis, even with moderate fever, cerebral disturbances may occur. The movements of mastication and deglutition as well as speech are made difficult and painful by the swelling. The muscles suffer a functional damage, the enlarged parotid lying as a mass below the branch of the lower jaw, hinders the backward motion of the food in chewing; the mouth can scarcely be opened. Under some circumstances the enlargement may reach so high a grade that not only solid food but even fluid is refused and the consequences of this become apparent. The proper care of the mouth, on account of insufficient opening of the mouth, cannot be properly carried out, hence a decidedly fetid breath occurs. Catarrhal stomatitis may appear. Occasionally the surroundings of the mouth of Steno's duct are reddened and swollen and the duct itself may be felt as a stiff band.

The salivary secretion in a number of cases is not altered; in others it is increased or diminished.

Displacement of the posterior lower auditory meatus, swelling of the external auditory meatus, and on the other hand of the Eustachian tube, lead to disturbance of hearing and produce pain which influences the sleep of the little patient.

Often in particularly well marked cases the movements of the head become painful; the head is held rigid and, as a rule, slightly inclined toward the

diseased side, besides it is somewhat retracted so as to lessen the tension of the muscles of the head; in a bilateral disease the head is held straight in a medium position, somewhat posteriorly, or even bent somewhat anteriorly.

Occasionally, as the nerve is implicated, facial paralysis is produced. This occurred in the nursling aged seven months mentioned above. DeR were distinct. In six weeks recovery occurred.

The frequency with which the second parotid is affected in the course of the disease varies in different epidemics. The most usual condition, in general, is that a few days after the swelling of one parotid the other is also affected, but this does not occur to the same extent as in the first gland; but epidemics also occur in which it is quite exceptional that the disease is not limited to one side.

Although completely afebrile cases exist, still, as a rule, in the course of parotitis there is fever. Even in the prodromal stage in a great majority of cases this occurs, although the rise in temperature is often slight and only noted in the afternoon, so that in case the other symptoms are not well marked it may readily be overlooked. With the appearance of the swelling of the parotid the fever rises, as a rule, not over 102.2° F., but there are also cases with a decidedly higher afebrile course, 104° F., 106.7° F., even lasting for several days and accompanied with prostration, apathy, somnolence and even convulsions, in some epidemics. After a few days, when the parotitis has reached its acme, the temperature falls to normal, occasionally quite suddenly, accompanied with sweating, even before the local process has run its course. The fall in temperature is interrupted and at first a new rise occurs, but not to the former height, if the disease attacks the other side. If relapses occur these renewed rises in temperature are noticeable, as well as with the appearance of complications a decided rise of temperature accompanied with chilly sensations. Thus the fever period, which usually ends in about seven days, may last for fourteen days and even longer.

The pulse frequency corresponds to the temperature in so far as it is not influenced by pain and restlessness.

In severe cases at the height of the disease enlargement of the spleen may be noted (Ewart) also swelling of the cervical lymphatics.

The duration of the disease in uncomplicated cases is in the main dependent upon the intensity of the glandular swelling. In medium severe cases this increases for three or four days and then after edema in the surrounding area becomes less noticeable and the glands are softer, normal conditions are gradually assumed. If the tension of the skin is high graded, bran-like desquamation occurs. In the ordinary cases the process is finished in from eight to fourteen days. In the severer cases this lasts longer and in the abortive cases the process is finished in a few days. In some cases the course is a very protracted and stubborn one. It may take from five to six days until the swelling reaches its acme and if the second gland becomes attacked this period may be even longer, whereas it usually occurs in from one to two days, occasionally after three days.

COURSE AND TERMINATION

The course and termination of the disease, as a rule, are favorable even in those cases in which complications occur. The parotid returns to the normal although it occasionally occurs that for a long time, for the most part in connection with surrounding lymph glands, it remains infiltrated and only gradually returns to normal. Occasionally functional disturbances lasting for some time are observed. Thus Eichhorst saw in a boy aged nine, for three months a decided hypersecretion (cured by atropin). Similar cases were seen by Simon and Prautois; Burton on the other hand saw a diminution in secretion, which was cured by galvanization. Suppurative processes which then only attack a part of the gland are in the main extraordinarily rare. In individual, particularly malignant epidemics, this unusual complication may become frequent, thus in the epidemic at St. Cyr, and in an epidemic observed in Berlin in the spring of 1825 by Hufeland.

The most peculiar complication of parotitis is *disease of the testicle*, which was even known to Hippocrates. This is frequent in men, exceptional in the aged, who in fact rarely suffer from parotitis, and occasionally noted in boys who are near puberty, in the ages of twelve and fourteen years. In earlier life it is extraordinarily rare, a fact to which Laghi called attention. Fabre's patient was nine years, Naumann's eight years. De Cernville saw orchitis in a patient aged four and Steiner even in a nursling, the only case of this kind.

It is interesting that occasionally orchitis may precede parotitis and that at times of mumps, *orchitis parotideae* may occur without parotitis being observed; a complete analogy to the condition occasionally shown in disease of the submaxillary gland in parotitis. The case of Bécère is characteristic. A boy aged fifteen, in whose school mumps was epidemic, was attacked by orchitis without parotitis, two of his sisters being attacked by parotitis.

The frequency of orchitis varies in individual epidemics of mumps and the appearance of orchitis is quite independent of the severity of mumps. Rizet even observed an epidemic in which, particularly in the milder cases, orchitis occurred. Patients with gonorrhea, as the observations of military physicians have shown, are by no means particularly predisposed to orchitis.

If orchitis occurs, the testicle usually swells some time between the sixth and ninth days of the disease, whereas the parotitis is already upon the decline, the testicle swelling two to three times its normal size. Usually it is the right testicle. In unilateral parotitis, according to Monti, the left testicle is affected. Simultaneously the temperature rises, often with an initial chill. In the testicle itself, there is a sensation of dull pressure, of tension, also severe pain. Neighboring organs usually remain completely free but they may also be implicated by thickening and swelling. Acute hydrocele may occur, and the scrotum may become edematous and painful. Bilateral disease of the testicle is decidedly rarer than bilateral parotitis. If the second testicle becomes affected this occurs after two to four days; the swelling of the testicle in general lasting from three to six days. This also, as the enlargement of the parotid, as a rule, returns to normal without further consequences; but it must be noted that this condition is not so benign, for particularly according

to the reports of French military physicians, in a comparatively large number of cases, atrophy of the testicle has been observed, which for the most part was only partial and not followed by impotence.

Occasionally prostatitis occurs; occasionally also urethritis and cystitis. Rilliet and Sanné noted in a school epidemic among 10 cases of orchitis, 5 with a yellowish tenacious secretion from the urethra.

In what the connection consists between the parotid gland and testicle, which forms the basis for the peculiar implication of the testicle in parotitis, and in what manner orchitis occurs has not yet been cleared up. Orchitis has been noted with particular frequency by military physicians, especially in France, in epidemics occurring in barracks, and this gives rise to the possibility that the germs have been directly transmitted to the urethra, finding their way upward into the testicle—an assumption which finds a certain support in the fact that in a number of cases urethritis is noted, but by no means in all.

In the female the genital tract is also implicated, but by no means so frequently. Besides vulval vaginitis, bartholinitis, swelling of the large labia, urethritis, menstrual disturbances, there occurs also, analogous to orchitis, disease of the ovaries. Voigt saw in a girl aged eleven, in the course of mumps, the right ovary swell to the size of a chestnut, being painful upon pressure. The mammary gland may also swell and be painful. Travel observed this disease in a patient aged fifteen, Rizet in a girl aged five. Occasionally in the male, *mastitis parotidea* occurs.

Guelliot noticed a transitory swelling of the thyroid gland. Occasionally, however, rarely, the implication of the tear gland on the one side as well as bilaterally has been noted with swelling of the upper eyelid, so that the tear gland could be felt resembling a hard kernel. Jacob claims to have noted a pancreatitis occurring acutely and subsiding in a few days, producing a sausage-like tumor, sensitive to pressure below the liver, accompanied by pain in the epigastrium, vomiting, fever (104° F.) in the course of mumps.

Albuminuria has been frequently noted and also cases of true acute infectious nephritis, sometimes of a hemorrhagic character (Pratolongo, Isham, Hensch, Croner and others). As a rule recovery occurred.

Among other complications which have occasionally been noted there are to be mentioned, endocarditis and pericarditis (Jaccoud, Grancher and others) terminating in recovery, ostitis, osteomyelitis, articular and tendon affections such as occur in the course of scarlatina and gonorrhea, but much more rarely and milder. Occasionally with erythema and various cutaneous affections (erythema nodosum, papulatum, urticaria, petechia). Severe disturbances on the part of the respiratory tract apart from the previously mentioned case of edema of the larynx, from which, per example, Pailhas also lost a boy aged eleven, have rarely been observed; on the part of the digestive apparatus, stubborn vomiting, severe colic, marked diarrhea, finally all terminating favorably.

Milder affections of the same belong to the picture of mumps, especially if fever is present. On the part of the nervous system there are articularly reports from French observers that occasionally in the course of parotitis and in connection with the same mental disturbances, delirium, convulsions and

meningitis occur. These complications occurred in the main in severe, markedly febrile, cases in neuropathic children (Comby), associated with orchitis. Lately Heubner in his text-book has mentioned an interesting case of this kind in which in a strong, intelligent boy aged thirteen a complete psychosis developed with complete disappearance of memory for former events and forgetting his surroundings, which after a period lasting several weeks of sleep and dream life, gradually terminated in recovery. Multiple neuritis (Joffroy) has been noted as after other infectious diseases, and in rare cases besides conjunctivitis severe affections of the eye, keratitis (Zossenstein), iritis (Collomb), retinitis (Hatry), neuritis optica (Tallon) with amaurosis.

It is noteworthy that apart from otitis media, on account of the immediate neighborhood of the diseased parotid gland, disturbances of the ear occur partly without a primary otitis media; severe labyrinthine disease without noteworthy prodromes, with unilateral or bilateral deafness; attacks of vertigo and headache may appear which give but small hope for the return of hearing (Toynbee, Pierce, Alt and others). Although these occurrences are rarer in children than in adults, still several cases have been reported in which children under thirteen have become deaf in the course of mumps.

All of these various complications, mentioned on account of completeness, do not play an important rôle in parotitis. Orchitis is the complication *κατ' ἐξοχήν*.

PROGNOSIS

The prognosis of the disease upon the whole and in the main may be designated as good, although occasionally epidemics occur in which severe cases accumulate. Even these in general terminate favorably. Fatal cases are extraordinarily rare. Among 58,331 cases of parotitis which were reported in Denmark from 1870 to 1894 Ringberg (Jahrb. f. Kinderhk., Bd. xlvii, page 313) only found 7 which terminated fatally, among these 3 children (2 in the first year of life). Nevertheless, as Leichtenstern quite properly emphasizes, mumps may become serious in that in scrofulous children it occasionally forms the starting point of serious diseases, particularly glandular supuration.

DIAGNOSIS

The diagnosis, as the result of the characteristic symptoms which parotitis furnishes, can scarcely be missed. When the lymph-glands in front of the ear, at the angle of the jaw, begin to enlarge rapidly, the surrounding connective tissue is involved in the inflammatory process and a doughy swelling arises, at the onset, before the skin reddens, before abscess formation becomes plain, the diagnosis of parotitis may be incorrectly made. This occurs, but may be avoided if it be remembered that in parotitis the groove between the mastoid process and the lower jaw becomes filled, a broad tumor forming in this region, that the parotid becomes sensitive to pressure, not, however, so painful as a beginning abscess. A confusion with secondary, so-called, metastatic parotitis is scarcely possible. This is observed in purulent inflammations of the mouth and pharynx, in diphtheria, particularly in severe typhoid, in fact in diseases, especially in acute ones, which go hand in hand with

severe prostration, such as the acute exanthemata, in puerperal sepsis of the mother and newborn, due for the most part to the entrance of pyogenic organisms from the contaminated mouth through Steno's duct into the gland, partly perhaps also from blood infection. Although here as in parotitis, the parotid gland itself enlarges and in this way the local symptoms show great similarity to mumps, especially as in metastatic parotitis, on account of apathy and somnolence, the pain may not be so marked, nevertheless the presence of the primary affection, the fact that the parotitis occurs upon one side, the slower development, the greater extent of the tumor and the tendency to abscess formation, assist the diagnosis into the proper direction. Difficulties in the clinical picture in mumps only occur when the submaxillary gland or the sublingual gland, without implication of the parotids, swells, or this condition precedes enlargement of the parotid, or if after the glandular swelling has returned to normal, complications, particularly orchitis, must be of value as diagnostic aids.

THERAPY

The treatment in general is very simple. In a majority of cases covering the gland, to keep out deleterious external substances, application of warm oil, covering with cotton, keeping the mouth clean by rinsing with antiseptic fluids, bland, mostly fluid diet, regulating the bowels, and if fever is present, rest in bed. In a great number of cases the physician is not consulted at all as the affection is known to be benign. Special attention is to be given to the care of the mouth. If the return to normal of the enlarged gland should be protracted, iodine preparations may be used, per example, inunction with iodine vasogen, painting with iodoform collodion (1-15), etc. If, exceptionally, suppuration occurs the gland is to be incised, great care being taken not to cut the facial nerve branches. In orchitis, rest in bed is necessary, elevation of the diseased organ, the application of cold or if this is not well borne, of moist warmth. All severer symptoms and complications are to be treated according to general principles. The fact that these conditions arise in mumps does not require a change in their management.

After all symptoms have disappeared, a few days after the parotid swelling has returned to normal, the children ought to be bathed. They may then leave the house and come in contact with other children. Although it is correct, that most frequently isolation is practised too late, because professional opinion is not consulted on account of the long period of incubation or the slightness of the affection, nevertheless the patients are to be isolated. In regard to the mildness of mumps, Henschel believes isolation to be unnecessary and Laveran is of the opinion that children should be exposed to the infection to protect them in later life from the complication with orchitis. Although mumps in childhood, in by far the greater number of cases, does not give occasion for the slightest anxiety, still the possibility must be considered that parotitis in youthful individuals, although very rarely, may take a severe course, may be complicated by nephritis, otitis media, etc., and may be the starting point of the appearance of scrofulous phenomena. To this may be added that on account of the limitation of the predisposition to the

disease the possibility exists that persons may remain spared from the affection. By immediate isolation of sick children in large institutions, schools, etc., a further distribution of the disease may be prevented. As we are dealing with an infectious disease in mumps, disinfection of all materials that have been in use and thorough cleansing of the sick room is advisable. It is well in regard to the mildness of the disease only to undertake the most necessary measures; all the more, as those about the patient, are not even inclined to do this, if inconvenience or cost be associated with these measures.

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PERTUSSIS, WHOOPING-COUGH, TUSSIS- CONVULSIVA

By A. BAGINSKY, BERLIN

IN observing a young child that is coughing, if the cough be accompanied by a peculiar loud, sighing inspiration, several points are to be noted by a careful diagnostician. If the cough is severe, forcible, paroxysm upon paroxysm succeeding one another and finally accompanied by a spasmodic laryngostenotic apnea, so that the face assumes a dusky hue and finally becomes cyanotic, the entire attack showing a threatening character, it is quite evident that such a child is suffering from pertussis, an infectious disease of childhood.

Two points should be noted at once, that a cough of this character presents an affection *sui generis*, and secondly, that such a child should be isolated, as it is suffering from a transmissible disease. This affection of childhood, which apparently presents a severe character, is the purpose of the present monograph.

GENERAL CLINICAL PICTURE

CASE HISTORY.—A boy, aged four, in whom at first glance no pathologic condition can be noted. The mind is clear, cheeks are red, perhaps somewhat rounder and fuller than is usually noted in children of this age, the child presenting, in general, the appearance of robust health. Pulse and temperature show nothing abnormal, nor does the character of the child's respiration; upon undressing it, however, it appears that the child, apparently in the best of health, does not show a condition of nutrition upon the rest of the body in harmony with the full face, above all, on account of the flaccid condition of its adipose tissue. The child, upon the whole, is not as well nourished as might appear at first glance, the fatty tissue is soft, flabby, the skin is quite dry, almost wrinkled upon the arms, abdomen and legs, and we cannot escape the impression that the face shows a somewhat bloated character, which renders it very probable that the condition of nutrition of the body is not as good as it formerly was.

In searching for the possible reason of this retardation in nutrition, we find that neither the temperature curve nor the condition of the urine nor the feces of the child furnishes a clue; only one thing may give us a point of support for this explanation and this is the report that the child suffers from severe attacks of cough, which are frequently accompanied by vomiting, that these attacks of cough and vomiting occur from four to ten times a day and even more frequently. If the child takes nourishment after an attack of coughing and vomiting of this sort, it may readily occur that the interval between the attacks of cough are not sufficient for complete gastric digestion, that is, for a definite removal of the food from the stomach to the intestinal canal. The parents report that the child has lost weight.

Physical examination shows normal conditions throughout. Everywhere, over the thorax, vesicular respiration, nowhere accompanied by catarrhal râles, nowhere abnormal dulness; on the contrary, if anything were noteworthy, the decrease in cardiac dulness, which is apparently due to the fact that the pulmonary tissue covers the heart from right to left, showing a lessened *volumen auctum pulmonum* is noticeable. However, the heart sounds are normal and pure; neither in the organs of the abdomen can anything abnormal be determined either by palpation or percussion.

In examining the pharynx and the mucous membranes of the child by means of a tongue depressor, placed over the dorsum of the tongue, the child has an attack of coughing and suffocation.

This attack has some special characteristics. It is noted that the cough is of quite unexpected severity. While the hollow cough becomes more superficial and shorter, paroxysm following paroxysm, the face of the child becomes dark red, the tongue is protruded, the eyes are prominent appearing injected and moist, lachrymation occurring; inspiration during the individual paroxysm of cough is insufficient, the child can scarcely breathe, and only from time to time, between the paroxysms, does a deep, hasty, sighing sound occur, a long continued inspiration; masses of glassy, moist, foaming mucus are brought up; this continues almost up to the point of complete exhaustion. Finally the force of the cough appears broken, the paroxysms become briefer, rarer, looser, the child resumes its normal color and appearance. But not yet completely; apparently the child is disturbed by a new sensation; it appears to suppress a tickling in the throat, it endeavors to swallow to master this; the facial expression becomes somewhat anxious. In fact the cough breaks out anew, this time even more severely than in the first attack. The child can scarcely breathe, so rapidly do the paroxysms of cough follow one another, so short are the pauses which permit inspiration, and now the cough is accompanied by retching, followed by vomiting, which evacuates the contents of the stomach accompanied by masses of glassy mucus, not without continued troublesome retching and occasional attacks of cough. Finally the child is free from cough but in a dreadful condition! Covered with perspiration, exhausted, pale and tired. The pulse has become soft, frequent, over 120 beats per minute. It is plain that this represents a characteristic of the disease, and it is easy to understand that if attacks of this kind occurring from five to six times during the day and perhaps more frequently during the night—for in fact the nocturnal attacks are more frequent and even more severe than those which occur during the day—are repeated, the nutrition of the child may very readily suffer. Thus we understand the contrast between the apparent fullness of the face, which in fact is puffy—it would be too much to say edematous,—and the condition of nutrition of the rest of the body.

PATHOGENESIS AND ETIOLOGY

Whooping-cough, pertussis or tussis-convulsiva, is a disagreeable disease and one which may extend for weeks and months, finally enfeebling the strongest children, becoming dangerous to younger ones but may even be serious in older children to such an extent that many years may pass before they regain their normal constitutional condition, even if no complicating affections threaten the life in older patients, which may readily be the case.

The disease unquestionably belongs among the infectious diseases; it is not very readily transmitted, but this certainly occurs by contact between children; however, this may take place, as I have observed with certainty, by means of third persons who come in contact with sick children, conveying it to those that were previously healthy. The contagium adheres to rooms, to fomites; it is actually one of those diseases which are readily distributed through a school. In truth the disease spares no age; it occurs in the youngest nursing as well as in adults, although children during the ages from one to four are most susceptible. I am able to give the following figures from my own observation: Among 2,650 cases admitted to the hospital in ten years the following cases were observed:

- 830, in the first year of life.
- 1,308, one to four years old.
- 502, four to ten years old.
- 11, ten to fourteen years old.

Although the number up to four years, in general, is somewhat greater than that between four and fourteen, the frequency of the disease during the first four years of life is comparatively much greater, so that there is certainly a predisposition for this age. It will be noted that nurslings are by no means exempt, as was formerly supposed; on the contrary, I have repeatedly had an opportunity of observing, in my consultation practice as well as in the hospital, that nurslings are frequently and very seriously attacked by this affection. Boys are almost as frequently attacked as girls; there is no difference in sex regarding predisposition.

It can hardly be maintained that season and weather influence the frequency of the disease. Whooping-cough occurs in summer to the same extent as in winter, with the difference that the winter epidemics are more tenacious and more serious, as complications on the part of the respiratory organs occur more readily in winter and thus produce a severer form of the disease.

The disease is an infectious, transmissible one.

Much discussion is noted in literature regarding the cause of the disease. The question of a pathogenic agent is discussed as much to-day as at any time; each day bringing fresh investigations, new discoveries—unfortunately too many—and what is even more serious, no two that coincide. I shall only mention, to complete the discussion, that all sorts of schizomycetes, such as fungi that grow upon orange-skins, have been supposed to be related to the disease, that long, anerobic rods (bacilli) have been looked upon as the pathogenic agent, and that for example, Afanasieff is said to have produced the disease artificially in animals with these rods. I must mention that a specific diplococcus, cultivated from the sputum, has been described as the pathogenic agent and that the numerous authors who have made these discoveries are still discussing the identity of all of these findings. Thus, lately, a small pole-bacterium, which occasionally occurs in short chains, described by Arnheim, which appears to be identical with one previously observed by Czajlewski and Hensel in culture and biological behavior; it is quite probable that in numerous cases of whooping-cough this bacterium may be present. Nevertheless there are many doubts regarding these findings, and above all the etiologic importance has not been proved. The relation of all these discoveries becomes even more questionable, since a new bacillus has been lately described by Jochmann, which is said to be closely allied to the influenza bacillus (Pfeiffer), perhaps is identical with it, and, as the author expresses himself, “must be first considered in investigating the etiology of tussis-convulsiva, as the bacillus is constantly found in the expectoration of whooping-cough during the convulsive stage.” I may further mention that Deichler, in the year 1886, found protozoa-like structures in the expectoration of whooping-cough patients, which he believed to be the pathogenic agents; and thus quite a number of microbes have been etiologically suspected from which a choice may be taken according to option, or, what appears to me to be more preferable, it is better to remain a skeptic, or what is even better, every physician should himself search for the concealed, mysterious germ of the disease.

It must not be thought that an attempt has always been made to clear the uncertainty of this curious disease from the standpoint of contagion. Moreover, an attempt was made originally by physiology to search for the causes

of the cough, to find the point of development of the disease. We know that the superior laryngeal nerve is the nerve which produces cough and that the posterior wall of the larynx, below the vocal cords, is the region from which most readily, intense cough may be produced. We have learned to recognize the severe reflex cough due to irritation of the nasal mucous membrane in which the fifth nerve is affected, and we were inclined to look upon these points as the actual seats of the pathologic changes which produce whooping-cough; the last mentioned area, all the more, as cases of whooping-cough are observed in which severe attacks of sneezing simultaneously accompany the cough. In fact we are able to observe, and this has been particularly described by Mayer-Huni and v. Herff, that the larynx, particularly, however, the entire posterior portion, the inter-arytenoid mucous membrane, shows a catarrhal condition and inflammatory changes; the nasal mucous membrane and the tracheal mucous membrane, so far as they are accessible to direct investigation, are the seat of quite decided inflammatory irritation and swelling during the course of the disease. Thus there is a certain anatomic basis for the disease—inadequate and unimportant in comparison to the severity of the symptoms—and in connection with our experience of the positive transmissibility of the disease we can hardly explain the condition differently, than by assuming that the disease is due to an infectious germ, causing catarrh of the upper respiratory passages, thus considering whooping-cough among the infectious, catarrhal diseases. Whether any of the previously mentioned microbes, that have been found in the mucous membrane inflammation, are the pathogenic agents or whether we are always dealing with the same one, which I believe to be extremely likely on account of the characteristic nature of the cough, cannot be decided in any direction at present.

Thus it is noticed how etiologic investigation, begun at the bedside, searching for the cause of a disease, leads us from clinical observation; this is quite natural in dealing with an infectious disease, the etiology of which has not been cleared up, for we are actuated by the thought, that with the discovery of the cause of the disease, the possibility of combating and controlling the affection will be attained.

INDIVIDUAL SYMPTOMS AND COURSE

The character of the disease, in the history just quoted, was uncomplicated; but particularly for this reason it was calculated to show the nature of true, uninfluenced whooping-cough. It was noted that the actual attack of cough was capable of division into two parts, that the first was followed by a second one, and I may mention that sometimes a third follows the second. This is characteristic of whooping-cough and the repetition of the attack is called “reprise,” or whoop; this hardly occurs in any other form of cough and from this alone whooping-cough may be recognized from other severe attacks of cough; thus from those due to enlarged bronchial glands, or that form of cough due to adenoid vegetations in the naso-pharyngeal space, etc. Whooping-cough, as a rule, does not at once begin with severe attacks of cough, still less with the characteristic “reprise.” The disease develops as a simple catarrh and this is also the mode in which the affection began in the patient whose

history has just been quoted. However, from the beginning the cough has an extraordinarily severe character; there is a peculiar, intense, severe irritation which brings about the cough so that the children become dark-red in the face while coughing, even if but few paroxysms of cough follow the irritation. There are no physical signs in the thorax which correspond to this severe cough. The respiratory conditions are normal, there are no râles or other signs of catarrh. More and more these irritative phenomena increase, becoming more severe, so that a few attacks of cough no longer relieve them and paroxysms of cough develop so that an actual attack occurs. Simultaneously the individual attack which now gradually takes on the character of the reprise just described, brings up a mucus, glassy, foaming secretion, quite in contrast to the usual condition in children who, as is well known, scarcely ever expectorate sputum.

Thus we speak of a *first (primary) catarrhal stage* of whooping-cough. Soon other symptoms are added which impress upon these attacks of cough a severe, threatening character. It will be observed that children under the influence of these expiratory attacks of cough gradually suffer for want of air, there is insufficient time for inspiration, moreover it appears as if expiration will not cease, due to the paroxysms of cough which constantly become shorter and more superficial. The face, which is more and more turgid, becomes dark-red, soon even cyanotic; the lips bluish, the small vessels of the conjunctival mucous membrane appear filled with blood, the veins of the face, of the temples and of the neck stand out prominently, like dark bands filled with blood; finally, respiration ceases entirely with the cough, in deepest expiratory position the thorax rests in apnea; finally, with a loud, sighing, whistling sound a new inspiration occurs and slowly, with profuse expectoration of mucus masses and vomiting of the contents of the stomach, deep inspiratory movements occur, interrupted by attacks of cough, completing the first part of the attack, followed by a second and even a third of almost like severity and of the same character.

This respiratory spasm and the apnea which are due apparently to the deepest expiration with closed glottis, have impressed the name *tussis-convulsiva* to the cough in this stage of its development, and the phase of the cough has been designated as the *convulsive stage*. Quite properly, for there are a number of cases in which in the same phase of the cough, during the apnea and in connection with laryngospastic conditions, actual clonic and tonic spasms occur of a severe epileptiform character with complete loss of consciousness and all the phenomena which go to make up the eclamptic symptom-complex. With these symptoms whooping-cough has reached the acme of its development; nor is there a limit for the number of the daily and nocturnal individual attacks. For weeks the cough may remain of the same grade of severity and 30-40-60 attacks may occur in the afflicted children which have a deleterious effect upon their nutrition, exhausting their strength, until unfortunately not so rarely, the organism succumbs to these conditions, or complications severely threaten the youthful life. It is true many recover, probably the majority of children affected even with the severest forms of the disease. However, among those who recover there are not a few who for life suffer from chronic invalidism, showing exhaustive conditions on the part of

the heart, such as dilatation of the cardiac ventricles, emphysema of the lungs, bronchiectasis with chronic catarrh, and bronchial adenopathy, besides all varieties of neurotic conditions and many other sequels which will be considered later on.

Finally, when the severity of the disease begins to decline, either spontaneously or from the influence of therapeutic or hygienic measures, true catarrhal symptoms become more and more prominent; the attacks of cough become less severe, the spasmodic symptoms less frequent and milder, the tenacious sputum more yellowish, nummular, purulent—*sputum coctum* of the ancients—whereas simultaneously catarrhal phenomena of all kinds may be noted in the chest by the presence of profuse râles, denoting the development of the *second catarrhal stage*. The attacks of cough become rarer and rarer, appearing only now and then in rapidly passing moments, so that after weeks or months, they only indicate that the child has recovered from a severe infectious coughing disease.

From this brief description it may be noted that the character of the disease is a severe one. Before considering the complications and sequels of whooping-cough some of the most prominent symptoms in the pathological picture will be described somewhat more in detail.

In observing a case of whooping-cough it will be noted that with every attack of cough the child has been forced to open the mouth quite wide and to protrude the tongue; in small children this is particularly marked and as they, as a rule, have very sharp and relatively well developed anterior incisor teeth in their lower jaw, the frenum of the tongue is readily injured upon the teeth when the tongue is protruded; thus under the tongue a small *sublingual ulcer* develops, at first showing a fibrinous coating, which for a while was looked upon as a characteristic symptom of whooping-cough. This is, however, not the case; it is nothing more than the expression of a mechanical disturbance which may occur in any disease accompanied by severe attacks of cough, and has nothing directly in common with whooping-cough and by no means is characteristic of it.

Another condition which is readily noticed is the fact that particularly small children with rickets, with their already deformed soft thoracic skeleton, suffer very severely under the influence of whooping-cough. Under the influence of the intense expiratory excursus the thorax almost appears collapsed during the dyspnea and apnea. It should be remembered that these children are readily attacked by catarrhal diseases of the lungs and bronchi, that they are very liable to laryngospastic symptoms and thus it will be easily understood how great the danger to life in these children when attacked by whooping-cough. As a matter of fact the majority of these poor, weak children succumb, if the disease be at all severe.

Another category of children who do not possess especial resistance of the blood vessels, in pale and weak anemics, the effects of these severe attacks of cough may be noted from numerous effusions of blood. In such patients it will be noted that hemorrhages occur into the conjunctival mucous membrane, into the subcutaneous cellular tissue, even from the ear, and, although rarely, from the bronchial mucous membrane, and from the lungs in the form of hemoptysis; hemorrhages into the brain shall be considered later on,

for they also occur. The subconjunctival hemorrhages which occasionally cover the entire eye and alarm the relatives of the child, as the eyes of the child attain a peculiar appearance, rapidly disappear by absorption of the effused blood, the condition being without importance, much less so than the hemorrhages from the ear or hemoptysis.

It is to be expected *a priori* and is readily understood that in the same manner, as a consequence of the mechanical disturbance from these severe expiratory explosions, other anomalies occur in the infantile body such as *umbilical hernias*, *inguinal hernias*, *prolapse of the rectum*, and general *cutaneous emphysema*, which although quite rare, I have myself observed and is worthy of note.

Quite a number of more or less bothersome disturbances complicate whooping-cough without actually having anything in common with the character of the same as an infectious disease; naturally they are not to be looked upon too lightly; and yet they are subordinate to the other complications which develop upon the infectious basis of the disease.

COMPLICATIONS AND SEQUELS

We shall consider some of the most important of this second group. It will be impossible for me to mention all of the complications which occur but I shall quote from my own experience and from the literature the most prominent of these.

CASE HISTORY.—A child, aged one and one-half years, almost moribund, with marked cyanosis even of the hands and finger-nails, dyspnea, in collapse, apparently unconscious, which but a few moments before was attacked by severe convulsions. In this condition the child was brought to the hospital and the physical examination reveals, bilaterally, especially posteriorly upon the left side of the chest, loud diffuse râles, particularly in the scapular region; in the same region bronchial respiration was noted. We were therefore dealing with a severe, diffuse bronchitis and with a large bronchopneumonic focus of the left lung, probably of both lungs. The temperature of the child was not above 101° F. The respiration was superficial and frequent, scarcely countable. The history showed that the child had been suffering from whooping-cough for some weeks; for a few days the symptoms of *inflammation of the lung* had been added, since which time the attacks of cough have become less frequent; in place of this, however, severe convulsions have occurred. We hardly hoped to save the child and this history is quoted to show that bronchitis and *bronchopneumonia* represent the severest danger in pertussis.

The conditions were little better in a second case: A boy aged one year; the history shows that for fourteen days he has suffered from whooping-cough. Three days ago fever began and upon admission to the hospital, a temperature varying between 101° F. and 103° F. was present with excessive dyspnea. In this case diffuse râles also were noted over the entire thorax and a quite extensive area of dullness over which bronchial respiration could be determined was found in the right scapular region. This child also had two general convulsions in one day; the child was unconscious and strabismus was noted. An unfavorable prognosis was given in this case. It is noteworthy that severe attacks of whooping-cough were observed in the child even in this condition.

Bronchitis and *bronchopneumonia* are in fact the two complications which develop from the infectious character of whooping-cough, and may perhaps themselves be designated infectious diseases, but when superadded to whooping-cough lend malignancy to the character of the affection and cause the death.

of young children. The danger in older children is not so great. However, the disease is severe enough and pulmonary inflammations complicating whooping-cough are to be feared under all circumstances; even in older children serious sequels remain: *Atelectases of the lungs* which are difficult to overcome; emphysematous areas at the border of the lungs; chronic bronchitis with a tendency to bronchiectasis, and what is more serious, with a tendency to softening of pulmonary areas under the influence of specific or saprophytic bacteria, such as the tubercle bacillus or the bacillus tetragenus and streptococci. Thus after years, *bronchiectasis* and *tuberculosis* may end the life of a child particularly when complete convalescence from the original disease has not taken place.

It will be noted that in the first case it was mentioned that the attacks of whooping-cough ceased with the appearance of pneumonia; this is frequently the case but not necessarily so, as is taught by the second case in which the attacks continued in spite of the pneumonia. I have already called attention to the importance of *convulsions*. In such instances they were the accompaniment of the general infection from pneumonia. But even without this, convulsions are serious additions of whooping-cough, and this is true even in older children, for this complication, which is very serious, often in a few days causes the death of the child. Probably here also the general infection is the source of the convulsion, for as we shall learn further on, the contagium of tussis-convulsiva has a toxic-malignant character. Convulsions may also occur from the combined action of several pathogenic agents under the influence of increased temperature.

Convulsions may also occur due to other causes, thus from an accompanying nephritis which gives rise to uremia. Many years ago, in a discussion in the Berlin Medical Society, I called attention to the fact that every infectious disease of childhood, even a subacute or chronic eruption, might be accompanied by *nephritis*; thus nephritis is by no means a rare occurrence in whooping-cough. I have lately had the opportunity of seeing several cases of nephritis occurring in the course of pertussis, fortunately without uremic convulsions.

CASE HISTORY.—A well developed girl suffering for a few weeks from a severe attack of whooping-cough frequently accompanied with vomiting. The face is somewhat turgid, the eyelids are swollen so that the bulbi can be seen with difficulty; the internal organs present nothing that is pathologic, however, the child is feverish, the temperature varying between 99.5° F. and 104° F.; the composition of the scant urine is conspicuous in that on some days it does not amount to more than 130 cc. with a specific gravity of 1,020; on other days amounting to 400 cc. The urine is turbid, of a light brownish red color, containing albumin, some few blood corpuscles, large numbers of casts mostly hyaline, beside numerous leukocytes. This presents a form of acute nephritis which could not be more typical than as a sequel of scarlatina. It is quite obvious that such a nephritis may also present a uremic symptom-complex, and I have noted this condition in a similar case in which a fatal termination occurred. The case was one of a well-nourished strong girl aged three who developed severe convulsions in connection with a marked case of whooping-cough; the spasms recurred frequently and did not yield to sedatives nor to venesection. The child hardly had an opportunity of recovering from its soporose condition, partly due to the influence of the dreadful attacks of whooping-cough which recurred twenty times daily and were accompanied by convulsions, partly also on account of uremic intoxication; for three weeks we had an opportunity of observing this case, which finally terminated fatally on account of the repeated con-

vulsive attacks. Unfortunately it was impossible for us to obtain an autopsy, so that the question had to remain open as to whether certain changes of the brain (hydrocephalus?) were responsible for the lethal outcome.

From this it is evident that nephritis represents a serious complication of pertussis and that we have good reason for devoting our attention to this complication.

Certain *anomalies of the heart* also require observation; in my text-book I mentioned the occurrence of sudden death due to cardiac collapse and unquestionably changes of the heart muscle play a certain rôle in this condition. If the cases are observed, which succumb after the disease has lasted a long time, degeneration of the heart muscle can often be noted. This was described by Silbermann many years ago. I have also observed this condition, but the minute study of these degenerative changes has not yet been concluded. It is evident that besides the probable direct toxic action of the poison of whooping-cough upon the heart muscle, the powerful stasis in the right heart which is due to the attacks of cough, is capable of damaging the heart muscle; all the more so if the children, under the influence of frequent vomiting and insufficient nourishment, suffer more and more in their nutrition, becoming feeble and anemic.

In the course and in connection with tussis-convulsiva the most remarkable and rare *diseases of the nervous system* occur which require careful consideration. They are not common, but I am able to speak from my own experience and report some very peculiar pathologic conditions.

The first case which called my attention to the peculiar disturbance of the nervous system, most probably due to the toxic effect of the poison of whooping-cough, was the case of the three year old daughter of a lawyer, who was brought to me in a most remarkable condition. A robust, strong child who had suffered from severe whooping-cough for weeks, suddenly presented a condition—I can scarcely express it differently—resembling the brute creation. Everything that characterizes a human being had disappeared in the child. Without speech, without sight and hearing, without taste, the child snapped at everything with which it came in contact in a stupid and insane manner; senseless and uninfluenced by its surroundings the child gave forth roaring sounds, feeling its way from place to place, running into everything and without the slightest sense of perception; even the property of mastication was lost and only with the greatest difficulty could the poor, unfortunate child, which had almost become brutal, be nourished. In this pitiable condition the child remained for weeks and only very gradually did a return to normal occur in that signs of the sense of perception by sound, curiously showing itself in attention to music, then of smell and sight reappeared. Gradually the sensorium became free so that the child showed a sense of recognition for its surroundings. After the ice had once been broken the return to a normal psychical condition was surprisingly rapid, and I was able to return the child to the happy father completely cured. The child showed no motor disturbance. The entire process affected the sensory and psychical spheres.

I observed two cases in the hospital which were not quite so characteristic

but nevertheless important; I have mentioned them briefly in my text-book but shall be a little more explicit at this point.

A boy aged three and a half, well nourished, was admitted in January, 1897. Three weeks before his admission to the hospital he had suffered from attacks of whooping-cough, which prior to admission were combined with general spasms (convulsions). Upon the day of admission there was high fever, almost 104° F., which disappeared in the next few days so that the temperature dropped to normal. In the following night severe spasms occurred beginning upon the left side, in the region of the facial nerve, and affecting the nerves of the arm, soon distributing themselves to the right side and finally, after a severe attack of cough, disappearing. After a number of relatively good days in connection with attacks of cough, severe crying spells occurred, apparently produced by hallucinations of fear, the child assuming an expression of decided fear, constantly exclaiming "to bed, to bed," whereas in fact he was in bed. Attempts at quieting him were entirely ineffective; only very gradually did he become calmer; however, the exclamations of fear and cries repeated themselves during the night; finally, the child slept, awoke upon the next morning with a clear mind and remained so in the further course of the whooping-cough, which gradually disappeared; the child remained free from similar attacks. The child was discharged cured.

In this case we were dealing with a psychical alteration closely allied to the well known *pavor nocturnus* of children, only with the difference that the terror did not occur during the night.

The third case closely resembled the first one described and occurred in a girl aged two, admitted in December, 1897. Prior to admission the child suffered for six weeks from whooping-cough accompanied by convulsions; under the influence of these conditions the child lost the sense of recognition for its surroundings and for this reason was brought to the hospital. The child was well nourished but showed itself as completely unconscious of its surroundings. The eyes, with the wide staring pupils were directed into space; with this there was rigidity of the muscles of the neck with slight opisthotonus; spasm in the somewhat spastic upper extremities and in the fingers, movements of mastication, deep sighing and occasional moaning, and loud screaming. The child had a normal temperature, pulse being from 96 to 100 in a minute. During the next days the child showed a more and more almost brutal, stupid condition. Bleating with suppressed voice; unmotivated movements of resistance with hands and feet, with a disturbed position of the extremities when a more quiet condition occurred; taking of nourishment in a greedy, hasty manner; complete apathy for the surroundings so that the child when taken up stared; when placed in bed it bored its face in the pillows while the trunk and buttocks were directed upward almost in an irregular knee-elbow position. Very gradually and slowly did the condition of the child improve and the mind become freer so that the child occasionally sat up and showed some sense of perception for its surroundings; when asked to shake hands it only slowly and hesitatingly complied "as if a veil covered the consciousness of the child," as the history remarked. With this the facial expression appeared serious and not childlike. Finally, the child became pleased with the ticking of a clock; slowly and with isolated sounds did speech return, at least to the extent that the child repeated words, speech up to then having disappeared completely. With this improvement of the mind the attacks of whooping-cough which had persisted and which were still quite severe, finally ceased and the child was discharged from the hospital in a greatly improved condition. The case recovered completely.

The similarity of this case to the one first reported is obvious, and as it is not likely that any serious anatomic lesion was the foundation of these peculiar psychic alterations, which, however, finally disappeared with relative rapidity, we may either consider an edematous transudation of the cerebral hemispheres

due to the influence of the severe attacks of cough, or a toxic influence of the brain due to the toxins of whooping-cough as the source of the nervous psychological disturbances. It is true in the last case, at the onset of the disease, there were certain symptoms pointing to a meningo-encephalitic irritation, such as rigidity of the muscles of the back of the neck, spasm, etc.; but on the other hand fever was absent so that a marked inflammatory infection of the meninges was not likely.

Nevertheless the cases are quite remarkable and medical literature is not rich in similar communications; however, other cases are mentioned which may be counted in this category and will aid to impress some of our observations.

Thus in literature there is a case of *sudden blindness* reported by Alexander and the author regards the cause of this condition to be due to a meningeal irritation produced by cerebral edema and so, also, other cases of disturbance in sight, due to probable cortical lesions of the brain, characterized as sensory affections under the picture of "soul blindness."

It is not surprising that under the influence of these severe attacks of cough, occasional *hemorrhages may occur into the brain* with the characteristic symptoms of *cerebral apoplexy*, hemiplegia, loss of consciousness with succeeding spastic unilateral paralyses, which only very gradually but nevertheless completely disappeared without producing a permanent damage to the affected child, but nevertheless are only with great difficulty corrected by orthopedic manipulation.

Stranger than these forms of paralysis are others due to serious lesions of individual areas of the brain and spinal cord, which either terminate fatally or produce a permanent damage to the infantile organism.

Thus I saw a case of *typical, ascending, Landry's paralysis* with a rapid, fatal termination in a boy, occurring in connection with whooping-cough; I still see him before me, a pale boy about seven years old, brought to my office, who collapsed completely in attempting to walk after a few staggering steps, and in the next few days being completely paralyzed with exquisite symptoms of a bulbar affection giving rise to difficulty in deglutition and respiration; thus there are individual cases of *spastic spinal paralysis*, of *encephalitis with paraplegic symptoms*, of *multiple sclerosis*, with beginning *bulbar symptoms* and later *spastic paralytic condition*, of *polyneuritis* with parasthesia, anesthesia and paralysis.

These sequels upon the whole are isolated when compared with the great frequency of whooping-cough in general, but they are calculated to show the affection as a serious and dangerous one.

I may refer, for other cases from my clinic, to an article by one of my assistants (May) in the *Archiv für Kinderheilkunde* in regard to nervous affections of this form.

In what manner these complications occur is entirely unknown on account of our lack of knowledge of the pathogenic agent of whooping-cough; it is hardly possible to refer all these conditions alone to mechanical causes, hemorrhages, edema and the like, and we are forced to think, the more such cases are observed, that similar to the condition in diphtheria, a toxic substance generated by the pathogenic agent circulates in the blood, as in the case of diphtheria, which affects the nervous tissue causing slight repair-

able, or also severe, unchangeable alterations; with the assumption of a toxic substance we are able to explain the peculiar observation which, as a rule, is noted in whooping-cough, the *hyperleukocytosis*.

MIXED INFECTIONS

As I have mentioned diphtheria, it is unfortunate that in whooping-cough other infectious diseases can be by no means excluded, that, moreover, combinations of pertussis with other infectious diseases bring about *mixed infections*, this being by no means of rare occurrence; thus we commonly find pertussis in combination with measles in young children, and also with scarlatina and diphtheria; the terrible condition may be imagined of a simultaneous diphtheria and whooping-cough in a child in whom, on account of a croupous, laryngostenotic affection a tracheotomy has to be performed, the cannula being kept in place and dreadful attacks of cough occurring—or in a case of measles, which is accompanied by bronchitis, the painful condition of whooping-cough being superadded. It is not to be wondered at, if these children succumb, with the symptoms of exhaustion or if pulmonary atelectasis or bronchopneumonia occur. Among the complicating diseases we also find, and not particularly infrequently in little children, *otitis media*, this being by no means a harmless and painless affection, for it frequently threatens life on account of its general effect when occurring in the course of whooping-cough.

After what has been mentioned it will readily be seen with what a dangerous disease we are dealing in younger children. In our statistics of infant mortality we reckon whooping-cough among those diseases which show a decided influence in the general mortality.

PROGNOSIS

From the statistics of the city of Berlin, only to mention this one city, we are able to note that in the years from 1890 to 1899 (ten years) the mortality in children from whooping-cough amounted to 4,868; among these more than half, 2,619, occurred in the first year of life. From the mortality tables calculated per thousand, in the population of Berlin, it will be noted that in the years from 1885 to 1896, 9.54 per thousand occurred from pertussis, greater than measles, which only amounted to 6.88 per thousand, and even more than scarlatina, which amounted to 7.83 per thousand. Thus there is every reason for fearing this disease.

The prognosis becomes more serious if complications are added, or preceding disease or constitutional anomalies, influence the health of the child; thus children with old caseous, tuberculous foci are in great danger, as well as children with old pleuritic adhesions, with still existing or previous rickets, syphilis, etc. Above all, the youngest children are threatened and for an infant there is perhaps no more dangerous serious combination than rickets with whooping-cough. It will be noted, from my explanation, that the direct danger to life is not all that is to be considered; that dangers may exist in other directions, in that many children become permanent invalids or only

recover with great difficulty, to finally succumb to tuberculosis; many retain pulmonary emphysema, a weakened heart, others nephritis, others all kinds of mechanical lesions such as umbilical hernia, inguinal hernia or nervous affections, paralysis, etc. In a word the prognosis of the disease is always serious.

DIAGNOSIS

The diagnosis does not give rise to difficulties. At the most, at the onset the disease may be difficult of recognition until the characteristic attacks of cough with a whoop and vomiting occur. If a genuine attack has ever been noted the diagnosis becomes certain; wherever there is doubt the signs of a severe attack of cough with an almost negative condition in the thorax, and the fact that the attacks occur particularly during the night, which is a very rare condition in simple catarrhal respiratory diseases, will aid the diagnosis. There are two varieties of disease with which whooping-cough may be confused: The cough which accompanies chronic pharyngeal catarrh and adenoid vegetations, and that form of cough produced by bronchial adenopathy. The first of the two affections may be readily recognized by an examination of the pharynx; the second is more difficult; nevertheless, even here, enlargement of the cervical lymph-glands and the physical signs obtained upon auscultation and percussion upon the posterior aspect of the thorax, offer points of support for the diagnosis; in the main, however, attacks of whooping-cough are so characteristic that they are even familiar to laymen and finally the presence of a hyperleukocytosis in doubtful cases will decide in favor of whooping-cough.

PROPHYLAXIS AND THERAPY

The early recognition of the disease is certainly of great importance. Unfortunately more for the friends and relatives of the patient than for the patient himself; for even with an early diagnosis we are incapable of aborting the cough or influencing its course; but the surroundings of the patient may be protected by removing and isolating the affected individual. This is of especial importance in schools, for we are thus able to prevent the patient from attending school and thus distributing the disease. As a matter of fact the prevention of contact and holding at a distance is the only prophylaxis in whooping-cough; there is no other protection of which I am aware. Even more than the prophylaxis is the therapy of the disease limited, and, as we may frankly admit, helpless.

Up till now there is no active therapy of whooping-cough, although every day, air bubbles of therapeutic successes are exploded. Unfortunately now, more than ever, pharmaceutical industry is busy in forcing remedies upon us; up till now, all without effect! Whether we prescribe reputed specific measures, which are none, like pertussin—a sweetened thymus extract or extract of chestnuts, antibacterial remedies of a general nature such as carbolic acid, thymol, resorcin and many others, whether these remedies are administered internally or externally, no matter, they are and remain without effect. The attempt has been made a hundred times to hang cloths dipped in carbolic acid over the beds of children; occasionally amelioration is said to have oc-

curred; according to my experience it is entirely without result; the same is true of inhalations of oil of turpentine, naphthalin, petroleum, nitrite of potassium, tincture of eucalyptus, gazeol steam, sulphurous acid, etc. This only tortures the children, we accomplish nothing with these remedies, for the disease progresses uninfluenced if it does not even show a deleterious effect as occasionally after the use of naphthalin, in that the respiratory organs show an inflammatory reaction and bronchitis develops.

I do not intend to mention the entire army of these useless remedies but only to speak of a few which have a somewhat favorable action. First is the extended use of fresh air; the more we are enabled to allow the children to remain in the fresh air the more readily do they overcome the disease; for this reason the children are sent into the woods, to the seashore and to the mountains, hence it is advisable to send the children to a different locality; unfortunately to the detriment of those localities to which the children are brought as the germs of the disease are carried from place to place. If in a cold climate, during the winter, it is impossible to use the treatment by fresh air we should see to it that the rooms of the children are well ventilated, the child often being removed from one room to another, to keep away the contagium which is distributed in this manner from the surroundings of the child.

Among drugs only two groups are to be considered; the one of a somewhat antifermentative, antizymotic character, and here quinin and quinin derivatives take the front rank. The salts of quinin in doses of 0.1–0.3–0.5 per dose two to three times daily, euchinin, which has no bitter taste in somewhat increased doses ($1\frac{1}{2}$ grams corresponding in action to 1 gram of the quinin salt) in some cases of whooping-cough have a decided action and serve simultaneously as a tonic, assisting the constitution of the child. With great care the preparations of salicylic acid, such as aspirin, antispasmin, are to be employed, as salicylic acid is capable of exerting a deleterious effect upon the heart muscle.

The second group of remedies includes all those which have a sedative effect and diminish irritation; here the first place is taken by morphia itself, then codein which perhaps is better borne by children than morphia; extract of belladonna, chloral hydrate, phenocollum hydrochloricum and the greatly praised antipyrin which occasionally is of decided effect; finally the entire list of bromin combinations, among which bromoform has lately taken the front rank. Bromoform, according to the age of the child, in from 3 to 5 to 10 drops three times daily, is a convenient method of administration and with some care also a harmless remedy, which is capable of diminishing the attacks of cough and thus perhaps to shorten the duration of the disease. With these remedies, which must be changed frequently, and combined with others, we will be able to offer some relief. Of all the other remedies formerly and lately advised I scarcely employ any, nor of the anti-irritative remedies which were advised upon theoretical grounds such as insufflation into the nose with benzol, calomel, boric acid, etc., and I only use these remedies if severe attacks of sneezing accompany the cough.

I need hardly add anything further in the treatment; in severe nervous conditions, in irritative conditions of the brain, meningitis, cerebral hemor-

rhage and other effusions of blood, in nephritis, in a complicating bronchitis and pneumonia, the remedies usually employed in these conditions are of use here; severe and repeated vomiting requires especial observation and besides small doses of morphia or codein the preparations of bismuth are capable of ameliorating and perhaps improving the condition. I need not mention nursing nor diet in this disease.

The children should be well nourished, according to their age and power of digestion. Meat juice, tropon, plasmon and foods of this kind may be used from time to time. Finally, after recovery from the disease hygienic measures must be employed to strengthen the child; after recovery a prolonged residence in a warm climate, such as a southern sea-coast, will certainly be of advantage if the physician is able to send his patient there.

ANGINA (TONSILLITIS) AS AN INFECTIOUS DISEASE

BY M. MOSSE, BERLIN

ANY physician of experience will know that a number of diseases may be referred to an affection, a tonsillar angina, which, perhaps, has not even been the subject of treatment. And this need not necessarily apply to more or less irrelevant conditions which may not trouble the patient at all, but to serious maladies which may require the most careful thought and action on the part of the physician. For this reason alone, it is certainly justifiable to devote to angina a special discussion, especially as we may succeed, by means of prophylaxis, in preventing a recurrence of angina or, by its proper treatment, simultaneously prevent the occurrence of affections which follow angina. But, even without this, angina—without considering its sequelæ—requires careful study, if only for the reason that the disease is so very common and may be easily confused with its much more dangerous concurrent affection, diphtheria.

Regarding the designation angina, this word has changed its significance in the course of time. Formerly it was the expression of one symptom, and at that the most important symptom, of a difficulty in deglutition and respiration; to-day angina is a pathologico-anatomical conception. This alteration in meaning is an interesting proof how, with a development of pathological anatomy in place of a symptom, a pathologico-anatomical conception has appeared, and how this latter has become completely absorbed by physicians, so that to-day no one any longer speaks of angina using it in its original conception. This law requires limitation; angina pectoris, for example, is not a pathologico-anatomical conception, but only the expression of a symptom-complex.

The fact just stated applies to conditions with which we are directly interested. As a proof, I shall quote the definition of angina given by Gerhard van Swieten,¹ quoting the opinions of Hippocrates, Celsus, Aretæus and others, in his celebrated explanation of Boerhaave's teaching: "By the word angina, which comes from the Latin word *angere*, there is understood, according to the usage of all physicians, those diseases which, by difficulty or by pain in those parts which serve in swallowing or in drawing breath, disturb one or both of these functions; but in the manner that the cause of these diseases is found above the stomach or above the lung." The translator² of Gerhard van Swieten remarks that the Germans have no expression to represent what the Latin scholar understands by "*angina*"; he translates angina with

¹ *Gerhardi van Swieten, Commentaria in Hermanni Boerhave Aphorismos. Tomus secundus, p. 618.*

² From the year 1767.

croup (Bräune) and heads the chapter in question: "Regarding angina or croup."

And to-day! Any text-book may be opened and, no matter how the opinions of the author may vary in other respects, angina will be found described as an acute inflammatory affection of certain areas of the gullet, as is shown by the vulgar designation "inflammation of the throat," as an inflammation which, in the majority of cases, may be referred to an infection. In reference to the extent of what may be regarded as angina, there is a diversity of opinion. Whereas some regard angina only as an affection of the tonsils, others identify the conception of acute catarrhal angina with that of acute pharyngeal catarrh in general. This latter view might be preferred, for the reason that an isolated inflammation of the tonsils is of relatively rare occurrence. We are to suit our definitions to morbid conditions as they actually occur and not to limit them to conditions which do not correspond with them.

In referring to angina, henceforth we understand an acute inflammatory condition of the tonsils, with the exception of the catarrhal form of inflammation, which not only affects the tonsils but also other parts of the pharynx. Before entering upon the discussion of the individual varieties of angina, some few remarks regarding the anatomy and physiology of the tonsils may be in place.

Anatomy and Physiology.—It is presupposed that we understand by adenoid tissue net-like connective tissue, the meshes of which are filled with leukocytes, and this designation is chosen for the reason that this variety of connective tissue occurs particularly in the lymph-glands. Adenoid tissue is found, further, in various parts of the digestive tract as well as in its beginning, the pharynx. The accumulation of adenoid substance in the pharynx has received the designation "lymphatic pharyngeal ring" by Waldeyer. Certain parts of this lymphatic pharyngeal ring are called tonsils, and especially those parts which, according to Bickel, are characterized by the following properties: 1. By a circumscribed form; 2. By diffuse infiltration with leukocytes and by containing follicles, also called secondary nodules, i. e., cellular infiltration in the form of nodules which in stained preparations have a paler centre, but toward the periphery show an especially close accumulation of cells; 3. By the possession of indentations covered with epithelium; 4. By the fact that the lymphatic tissue closely approaches the epithelium and perhaps still contains acinus glands.

These conditions are fulfilled by an accumulation of adenoid tissue in the following areas: 1, at the roof of the pharynx in the form of the *pharyngeal tonsil*, *tonsilla pharyngea*, *Luschka's tonsil*, an organ that retrogresses with puberty; 2, in the posterior portion of the space formed by both palatine arches; these are the *palatine tonsils*, *tonsillæ palatinæ*, the *tonsils sensu strictiori*. To these must be added 3, according to the nomenclature adopted by anatomical associations, the entire portion of the root of the tongue, the follicular glands of the tongue, which are known as the *lingual tonsil*, *tonsilla lingualis*. Without entering more minutely into the histological structure of these organs, we must especially mention, above all, a common finding. It is this, that the enveloping endothelia of the tonsils is invaded by numerous

leukocytes; this occurs in the manner that they dilate the spaces between the epithelial cells, producing a sort of empty space and then, partly encroaching directly upon the superficial epithelium, cause its desquamation. As the result of this, the superficial surface of the tonsils is covered with numerous leukocytes. The discovery of this important process is in general associated in Germany with Stöhr, and this reference will also be found in all books relating to the subject. However, the credit of having discovered and first called attention to these diseases unquestionably belongs to Renaut.¹

Have these processes physiologic importance? With this question we enter upon the discussion of the physiology of the tonsils and here it must be primarily stated that these organs, by the possession of glands, have importance in rendering the bolus of food moist. In reference, however, to the other point previously mentioned, we only know at this time that the leukocytes which have emigrated are identical with the corpuscles of the saliva. This naturally does not answer the question but only postpones it. It is possible that the emigration of leukocytes is important in the digestion of carbohydrates, as the leukocytes possess a sugar-forming ferment. This is the opinion of Rossbach, who further found that the palatine tonsils and the lingual tonsils have a much more powerful sugar-forming power than, for example, the mucous membrane of the tip of the tongue which is free from adenoid tissue, and that the lingual tonsil has this property to a greater extent than have the follicular glands of the tongue.

The importance of the emigration of leukocytes has been looked for in their property of rendering bacteria innocuous in that the entrance of microorganisms is prevented. This view is natural in connection with the general assumption of the protective power of leukocytes. In this especial instance this theory is probably incorrect; for no one has been able to demonstrate that individuals in whom the tonsils are removed are more readily and more intensely affected by infectious diseases than are others, and vice versa! If the tonsils were absolutely protective organs, it would be impossible for anyone to speak of tonsillitis as one of the most frequent infectious diseases.

A simple reflection may explain in general how the entrance of bacteria into the tonsils occurs, its sinuate structure naturally favoring this entire process. By the fact that the enveloping epithelium is partly desquamated, as previously mentioned, there is a plentiful opportunity in this region for the colonizing of bacteria. Thus, the importance of the Renaut-Stöhr's discovery is much greater for pathology than for physiology. But as plain as this process is in general, so little do we know of its consequences. How do the bacteria enter into the structure of the tonsils? Are they carried along passively? These are questions which can by no means be answered with certainty. Perhaps the act of deglutition plays a part, in that it mechanically forces the bacteria into the tonsils.

As little as we can give an explanation of the entrance and distribution of bacteria with certainty, so clear on the other hand are the pathological processes as such, upon which we shall enter in discussing the clinical picture. First, however, a word regarding the limitation of the conception of the disease. We have stated, that we understood by angina an *acute inflammatory*

¹ Traité d'histologie, 1897, vol. ii, p. 484.

affection of the tonsils, and it should be stated whether this refers to all the tonsils, i. e., to the pharyngeal, palatine, and lingual tonsils. In this connection, only inflammation of the palatine tonsils is to be regarded; then inflammation of the pharyngeal tonsils, and, finally, those of the lingual tonsils. It will be noted from the following description, that the conception of angina in practice does not always coincide completely with the definition just given.

We shall first concern ourselves, and this principally, with **inflammation of the palatine tonsils**, which in a restricted sense is designated *angina tonsillaris*.

We may recognize two principal varieties which are to be considered in practice: first, the catarrhal form; second, the purulent form in which two subdivisions are to be described.

Catarrhal Tonsillitis.—In regard to catarrhal angina, the inflammation is not limited to the tonsils, as has already been mentioned, but usually affects the mucous membrane of the entire pharynx. Often again not only is the entire pharynx implicated, but there is an involvement of the nose, the naso-pharyngeal space, the pharynx, the larynx and even the trachea, so that we then speak of a *catarrh of the upper respiratory passages*. In this condition the most manifold variations occur.

Patients who are attacked by an acute pharyngeal catarrh, in the majority of cases, have a painful sensation in the pharynx, a feeling of rawness, in milder cases only an unpleasant, scratching sensation. Deglutition is difficult, even upon the so-called "empty swallowing."

Some remarks regarding the examination of the pharynx may be in place. The most important point consists in illuminating the posterior pharyngeal wall. For this purpose, a mechanical depression of the tongue with a spoon or tongue depressor is necessary. In children, if no suitable instrument is at hand—which may occur—the tongue may simply be pressed down by the finger. Some persons possess the faculty of opening the mouth in the manner that depression of the tongue is unnecessary, as the pharyngeal space may be seen without difficulty. Sunlight or an artificial illuminating apparatus may serve as the source of light, the patient must be placed in a position so that as much light as possible falls upon the posterior pharyngeal wall. This is possible by direct illumination or by means of a reflector, in the former the source of light must be brought in front of the mouth of the patient, in the latter, the indirect method, behind the head of the patient, so that the reflector may catch the light and in this manner illuminate the pharynx.

As simple as such a procedure is, it is nevertheless necessary to have some practice in an examination by means of a reflector. If the physician has not had this practice, it is well for him to attain it, for if he has this skill, it is easy in connection with it, to learn to examine the larynx.

If now the pharynx is examined in this manner, different areas of the mucous membrane, or even the entire pharynx as far as it can be seen, are red and swollen. If the swelling affects particularly the follicles, they appear as yellow nodules and it is characteristic of them that they are situated below the mucous membrane and therefore cannot be removed; sometimes markedly dilated vessels are observed.

Catarrhal angina in the majority of cases affects youthful individuals

among whom there are some who are so predisposed, that it only requires a slight change in temperature or a slight walk in the street against the wind to produce the disease. In mild cases the affection runs its course without fever, disappears in from a few hours to a day or two; however, occasionally, and especially in children, catarrhal angina begins with a chill and fever; then the temperature may reach 102.5° F. and above. But even in these cases the affection runs its course in a few days.

In the **purulent form** of tonsillitis two subvarieties may be differentiated, a variety in which superficial pus formation occurs and one in which the production of pus occurs in the deeper tissues. In the former, the superficial pus formation, this is due to an accumulation of pus in the lacunæ of the tonsils. This is the condition which is usually designated as **angina lacunaris**. Formerly a follicular angina was spoken of. This designation, however, is inexact, because the word follicle, as already mentioned, is to be reserved for the characteristic round-cell conglomeration beneath the mucous membrane; for this reason it is well to drop the designation follicular angina entirely. Lacunar angina is a disease which shows all of the characteristic phenomena of an infectious disease. This is favored above all by the clinical course of the affection. Thus, in the midst of complete health or after a stage of brief prodromes consisting of headache, lassitude, anorexia, the child or the adult is attacked by severe fever, and in the same family frequently several persons are attacked one after another in the course of a few days, and thus all members of the household may be attacked in brief intervening periods. This alone proves that lacunar tonsillitis is an infectious, contagious disease, and as valuable as bacteriological investigations may be in deciding the question whether angina is an infectious disease, the clinical condition of the patient already gives sufficient points of support. To this may be added that, as Friedreich has determined, the affection is accompanied by an enlargement of the spleen, an interesting finding in a theoretical respect, although this does not occur in all cases. In general, the clinical picture shows itself in the following manner: Usually with severe fever—the thermometer may reach from 102.4° F. to 104° F.—marked disturbances in general health are noted; increased rapidity of the pulse, swelling of the lymphatic glands behind the angle of the jaw, and great difficulty in deglutition. Sometimes these symptoms are so severe that the rest at night is disturbed. The mouth is open, the voice has a “throaty” character and upon inspection of the pharynx it is found that, besides reddening or swelling of one or both palatine tonsils, they are covered with whitish or yellowish-white, purulent punctiform areas, the number of these varying greatly. Upon closer examination it is noted, during the stage of onset, that these areas fill the lacunæ of the tonsils. This condition may either disappear on the next day and the general phenomena also show improvement, or a dissemination of these purulent clogs occurs, so that they are no longer limited to the lacunæ but coalesce. In this manner the condition appears as if it consisted of a primary connected mass and the physician, who only sees the patient in this later stage, cannot determine at first sight, that only a coalescence of individual plugs has taken place. Thus, it is quite natural, that in this distribution of the throat phenomena the formation of primary connected membranes may be simulated. The exclusive

implication of the tonsils, however, is characteristic, as is also the absence of involvement of the adjoining parts of the pharynx. If the attempt is made to remove these deposits, this is easily accomplished, as a rule, without showing a marked loss in substance after removal.

Upon the third, or at latest, upon the fourth day, the picture just described changes. With an improvement of the general condition, the decline in temperature goes hand in hand, and we are often astonished if upon the third day even, the tonsils and their surroundings, still being red and swollen, are found free from deposit, while upon the preceding day, these connected masses were seen and the physician had not as yet completely determined whether he was dealing with a simple lacunar angina or not. Gradually the enlarged lymph-glands behind the angle of the jaw decline in size; it, however, occurs not rarely even after a mild angina, that for a long time afterward there is still pain, which is spontaneous or especially produced by pressure of these enlarged glands and this swelling may even cause great anxiety to the patient who may not have consulted a physician previously. Thus, tonsillitis runs its course in many cases without complications, apart from the fact that for a long time some weakness and lassitude remain, the expression of a recovery from an infection. But the disease as such terminates in recovery and only rarely does it occur that the malady terminates fatally, i. e., without further sequelæ occurring. Thus in the Charité in Berlin, during the years 1890 to 1900 about 1,800 patients were treated in whom the diagnosis tonsillitis and lacunar angina was made and only 12 terminated fatally, therefore a very small percentage, less than 0.7 per cent.

Lacunar angina is an affection which may attack the same individual repeatedly. As a resulting condition of recurring attacks of angina, hypertrophy of the tonsils must be regarded; this is especially the case in children, who, as is well known, frequently suffer from this condition. By this it is by no means meant to imply that hypertrophy of the tonsils always occurs in this manner; on the contrary, some persons have never or perhaps suffered but once from inflammation of the tonsils and have hypertrophied tonsils. On the other hand, not rarely, an atrophy of the tonsils occurs after repeated attacks of inflammation.

If one of the purulent plugs or a collected deposit in lacunar angina is microscopically examined, there are found in the mechanically removed areas, pus corpuscles, epithelial cells, detritus, and, above all, numerous microorganisms. As we are dealing with an accumulation of pus, it is quite natural that the usual pyogenic agents, streptococci and staphylococci play an important rôle here, and, in fact, the investigations which have been especially undertaken by Bernhard Fränkel have resulted, in by far the greatest number of cases, in discovering streptococci and staphylococci. Besides, a great number of other organisms have been found in systematic investigations, for example, pneumococci and pneumobacilli, bacterium coli communis, pseudodiphtheritic bacilli, micrococcus tetragenus, coccus conglomeratus, even the various forms of saccharomyces and mold fungi.

As many of these organisms are constant inhabitants of the oral cavity, it must be assumed that—for any reason by some favoring circumstance—a virulent condition of these germs arises.

In general, it must be said that the true importance of these findings must be determined by experimental investigations, as interesting as they may be. Lexer¹ succeeded, by infecting the oral and pharyngeal cavities of rabbits, in producing artificial local infection of the tonsils particularly. He found in animals, after twenty-four hours, that had succumbed to the infection, collections of cocci in various arrangements immediately below the epithelium, as well as in the deeper situated areas. Lexer experimented successfully with highly virulent streptococci in rabbits, after Ribbert had shown previously that by injections of bacilli of intestinal diphtheria of rabbits, the possibility of an infection by way of the pharynx could be experimentally determined. Lexer found further on, even a short time after the introduction of the pathogenic agents into the oral cavity, cocci in the internal organs and later in plentiful amounts in the blood and it was found that the port of entrance for these germs was the lymphatic apparatus of the pharynx, and principally the tonsils.

The investigations, according to this, also show an experimental explanation for the connection of angina and its sequels. Primarily, the very frequent clinical observation is to be thought of, the connection of lacunar angina with acute articular rheumatism. In general, the credit of having called attention to this circumstance is attributed to Trousseau and his pupils, it is, however, interesting to note, that the celebrated clinician Bouillaud² has referred to it, from which it may be concluded that a connection between the above mentioned diseases was known without, however, Bouillaud having distinctly expressed the connection. Thus, he refers to a young man who was attacked by acute articular rheumatism, that he suffered five days previously from a throat affection and in another clinical history, that of a sixteen year old girl, suffering from acute articular rheumatism, he reports upon one day having noted: "Un peu de rougeur et de conglomement des amygdales avec exsudation jaunâtre à la partie supérieure de celle du côté gauche." During the eighth and ninth decade of the last century, the previously mentioned condition has been the subject of numerous investigations on the part of American, English and French authors, and Whipple mentions, in 1888, in a report, a collective investigation for the British Medical Association, tonsillitis as being the primary affection preceding acute articular rheumatism. In Germany, the credit of having called attention to this connection belongs particularly to Buss, Suchanek, Gerhardt and others. Lately, this previously mentioned connection has gained further interest by the experiments of Fritz Meyer and Menzer³ who succeeded, by injecting in animals, streptococci which they had cultivated from a case of tonsillitis, in producing a similar clinical picture to that of human articular rheumatism.

Whether we are to look upon acute articular rheumatism with Sahli as an attenuated pyemia or not, this much is certain and must be especially considered in connection with the interesting effect of angina and other diseases, that in conjunction with angina a fatal sepsis and pyemia may develop. Such cases have been described in relatively large numbers and find their

¹ Archiv für klin. Chirurgie, Bd. liv., 1897.

² Clinique médicale. Tome deuxième, 1837.

³ See Verhandlungen des Congresses f. innere Med., 1901.

experimental analogy in the previously mentioned investigations of Lexer. Without explaining or desiring to elucidate the question, why in one case an infection with pyogenic organisms produces a general disease, and in others a special purulent affection appears, attention must here be called to the point that in connection with an angina, as well as in general sepsis, local pus formation may occur in areas which are distant from the port of entrance of the generators of the inflammation. Thus, after angina, ulcerative endocarditis and osteomyelitis have been seen to develop and Buschke has observed a purulent condition in a subcutaneous fracture after the appearance of an angina.

In this connection, the appearance of thrombosis and embolism during the course of angina must be mentioned. Bouillaud described a fatal case of tonsillar angina in which the necropsy showed the presence of thrombi in the right heart, which continued into the superior and inferior vena cavæ, into the jugular vein and the pulmonary artery; small thrombi were also found in the left heart and in the pulmonary veins.

Of great practical importance, further, is the combination of an angina with otitis media. Whereas it is not necessary here to assume the transmission by the blood or lymph channels of the pyogenic agent in this mechanism, the conveyance of the pus-forming germ from the primary point of disease may be thought of, if those not infrequent cases are regarded in which after an angina, inflammations develop in other distant organs besides those previously mentioned. Here, above all, pleurisy must be considered, the serous as well as the purulent variety; however, some authors also consider the possibility of the tonsils only as the means of entrance of a renewed infection. As the case may be, both possibilities are suitable as an explanation for another also very important complication, the nephritis. It is not rare that in connection with angina an acute nephritis of brief duration develops, which in itself may be the cause of a very insidiously developing chronic nephritis, in which, finally, contracted kidney may arise, which the physician discovers accidentally, when a disturbance of compensation appears. This connection is not infrequent, and impresses upon the physician the importance of examining the urine of his patients repeatedly for albumin after an attack of tonsillitis. By this, he will save himself and his patient unpleasant surprises.

The cases in which in connection with an angina an inflammatory or purulent affection of the appendix develops¹ must be explained quite differently. Here it must be assumed that the pyogenic agent by means of swallowing has reached the lower portions of the digestive tract directly. Naturally, here also the other explanation that assumes a distribution by means of the blood and lymph channels cannot be absolutely put aside, although it is less probable. In favor of the first explanation is the circumstance that the appendix contains adenoid tissue and by this means, similar to the tonsil with its follicles, is especially suited to infection on the part of the intestinal cavity. This comparison between the two organs has in fact been made and Sahli speaks directly of perityphlitis as an "angina of the vermiform process." These remarks are made in passing and only explain why, in fact, it is likely

¹ Compare *Kretz*, Wiener klin. Wochenschr., 1900.

that in connection with tonsillitis a disease of the appendix may develop, which arises by means of the act of deglutition.

According to the explanation given up to now, it might appear as absolutely certain that in angina and its complications microorganisms alone play a decisive rôle, that phenomena of intoxication do not appear, as, for example, in the case of diphtheria, in which we ascribe a part of the clinical phenomena to the toxins formed by the bacilli. Regarding the question of toxin formation of the pyogenic agents, streptococci have been especially searched for. Although this question has not been definitely decided, it must be said that the majority of the investigations have proven negative. Further, after recovery from diseases that are due to streptococci, no anti-bodies could be determined, we must rather agree with the negative opinion, as is done by Hilbert¹ upon the basis of some of his latest investigations. We will, therefore, have to say that for the present the proof of toxin formation from streptococci has not succeeded and that, therefore, we have no cause in affections produced by streptococci, such as angina, to assume an intoxication.

After this description of the clinical course and complications of angina lacunaris, a few remarks regarding differential diagnosis may follow. Above all, as already mentioned, diphtheria must be considered. In the majority of cases the mode of deposit as well as the distribution of the affection is decisive, especially if the physician is in a position to see the patient upon the first day of the disease. Briefly, in lacunar angina we are dealing with a yellowish deposit that upon removal shows but very slight loss of substance; in diphtheria, on the contrary, the color of the deposit is more grayish, it is more firmly adherent to the tissue beneath and is much more difficult to remove. Further, it is extremely rare that in angina an implication of the process occurs upon the palatine arches so that even here there is an important differentio-diagnostic point. In diphtheria, on the other hand, the adjacent parts, the palatine arches and the uvula are rarely spared. The course of both affections also is different, first there must be mentioned again that angina is over in from two to three days, diphtheria, on the contrary, in this period of time only makes progress. Of great diagnostic importance is the fact that the fever which accompanies angina sets in abruptly, whereas in diphtheria the fever rises gradually, and the thermometer in rare cases only shows a higher temperature range than 102.5° F. In connection with the high fever which accompanies angina is the appearance of acetone in the urine—at least very probably—to which Blumenthal² has recently called attention. Blumenthal found in 67 cases of angina, acetone 41 times in the urine, on the other hand, it was never noted in 36 cases of diphtheria; Legal's test was employed with non-distilled urine. This finding may probably explain that in angina a marked decomposition of albumin occurs, the expression of which is the presence of acetone in the urine.

Up to the present I have said nothing of the diagnostic need of bacteriological investigation in the differentiation between angina and diphtheria. Without going into details, I may give my opinion that in the great majority

¹ Chemische und medicinische Untersuchungen. Festschrift für Jaffé, 1901.

² Charité Annalen, 1902, Bd. xxvi.

of cases bacteriological diagnoses are unnecessary and that the diagnosis can be decided upon from the clinical findings alone. It is interesting to note that in regard to the one point that is of importance in practice, whether or not we are to inject diphtheria antitoxin, even according to Behring¹ the antitoxin treatment is not to be made dependent upon the bacteriological differential diagnosis, and regarding the second question which is put to the physician, whether cases which are suspicious of diphtheria are to be isolated or not, in all doubtful cases this should be answered in the affirmative.

Briefly, the conditions are these: In the majority of cases clinical observation is sufficient, in those relatively rare cases in which a clinical diagnosis between angina and diphtheria is not possible, antitoxin should be administered. In this manner we will never do harm and very frequently great good.

In the differential diagnosis of angina-like conditions there must be further regarded substances which are known as *tonsillar* plugs, i. e., cheesy masses deposited in the lacunæ, which consist of inspissated secretion which are harmless and do not produce any disturbance; further, the so-called *tonsillar calculi*, deposits of salts in the tonsils, which also have the same yellowish color that is peculiar to collections of pus in angina. It is assumed that tonsillar stones are the consequence of lacunar angina and consist of inspissated pus. Against this, the fact has been pointed out that these tonsillar calculi are not situated in the lacunæ but in the tissue of the tonsil. As, however, the stone-like plugs never cause fever, the differential diagnosis between these conditions and angina is very easy. However, it must be mentioned here that tonsillar calculi, by producing irritation in their surroundings, frequently give rise to tonsillitis.

Further conditions occur which have been inaccurately designated *herpes of the pharynx* also as *angina herpetica*. These are vesicles which are found upon the mucous membrane of the soft palate, the palatine arches and the tonsils, frequently occurring simultaneously with herpetic vesicles upon the lips and in other parts of the face. This affection, under some circumstances, might be confused with lacunar angina, especially if it affects the tonsils, in that it may produce similar symptoms, fever and difficulty in deglutition. However, closer investigation shows that we are dealing with vesicles which disappear in the course of a few days, partly by forming small ulcers which heal rapidly. There is still to be mentioned *mycoses of the pharynx* (B. Fränkel) which, being localized upon the tonsils, may resemble angina, generally, however, running its course without fever and disturbance of the general condition. The differential diagnosis of these conditions is easy; if the white flakes are removed the microscopical demonstration of fungi is readily obtained. It may be mentioned in passing that the treatment of mycoses consists in the use of nicotin, for example, in the form of tobacco smoke.

Finally, the occurrence of angina in various acute infectious diseases must be recognized; the more minute description of the condition will be found under each disease. This occurs particularly in *scarlatina*, more rarely in *measles*, *variola*, *varicella*, *influenza*, etc. Every case of well marked angina, especially in a scarlet fever epidemic, must give rise to the suspicion that it

¹ Diphtheria in "Bibliothek v. Coler," 1901.

is a part phenomenon of scarlatina. In general it is characteristic of the pharyngeal phenomena in the infectious diseases that they are almost never limited to the tonsils, but simultaneously implicate other parts of the pharynx especially the palatine arches.

As the previously mentioned affections are accompanied by an angina, the primary affection often being introduced by it, it is probable that the tonsils are to be looked upon as the port of entrance for the pathogenic agent of these diseases.

The condition designated *angina syphilitica sive specifica*, which is also an implication of the organs of the throat, occurring in syphilis, must be briefly mentioned; the details will be given elsewhere.

The *prognosis* of lacunar angina may be gathered from what has been previously mentioned; the therapy will be considered in connection with the treatment of other forms of tonsillitis.

We now enter upon the discussion of a deeper-lying purulent process of the tonsils. We then speak of **tonsillar abscess** (*angina tonsillaris abscedens*), which is comparatively rare compared to the far more frequent form and, for this reason, of more practical importance, peritonsillar abscess, i. e., collections of pus in the connective tissue between the tonsils and palatine arches. In both conditions, especially in peritonsillitis, high fever is almost always present, the patient complains of severe pain in deglutition, speech is difficult, the mouth can frequently only be opened with the greatest difficulty. Then the enlarged tonsils are observed as a prominent tumefaction and the mucous membrane of the soft palate is greatly inflamed. If the disease develops to a more marked extent edema of the surrounding parts, especially of the uvula, occurs. Thus, it is often difficult to gain a correct insight at the first glance. The palpating finger, however, notes fluctuation over those areas in which the mucous membrane is especially swollen. This is usually the region above and in front of the tonsil. If the patient is not seen by the physician in this stage the pus discharges itself externally about a week after the onset of the disease. The process may be distributed to the neighboring connective tissue also and thus produce the most dangerous conditions. This is, however, quite rare, as even the most indifferent patients, on account of the severe pain, are forced to consult a physician.

Here also it is naturally a question of disease produced by pyogenic agents, as well as in the disease inaccurately designated as **angina phlegmonosa**, as in this condition we are not dealing with a phlegmonous inflammation of the tonsils but mostly with a phlegmonous process of the tonsillar tissues, i. e., an infiltration which is distributed from the surface and does not terminate in abscess formation. This is often a disease terminating fatally, showing severe general phenomena, and an especially serious complication is the distribution of the phlegmonous process to the cellular tissue of the throat, the affection then being known as *angina Ludovici*; further, edema of the glottis with its consequences may arise.

Still a few words regarding inflammation of the pharyngeal and lingual tonsils. In general, it may be said that inflammation of these organs resembles that of the palatine tonsils, naturally with a limitation, produced by the ana-

tomical situation of these organs. For these reasons we may be brief in our description and, further, for the reason that the practical importance of these diseases, compared to those of the palatine tonsils, is exceedingly slight.

In **inflammation of the pharyngeal tonsil** we may differentiate a catarrhal and a lacunar form. Catarrhal inflammation of the pharyngeal tonsil is naturally only a part phenomenon of disease of the upper respiratory passages; in other cases it may appear as an isolated disease. In the main, as well as in the lacunar inflammation, it is a disease of youthful age. This is naturally in connection with what has been mentioned previously, that the pharyngeal tonsil shrinks with puberty. Lacunar angina of the pharyngeal tonsil clinically resembles angina of the palatine tonsil in so far as it also begins with fever, frequently preceded by chills, enlargement of the lymphatics, and constitutional symptoms. Speech is nasal, i. e., it is noticed that there is an obstruction to the passage of air through the nose and, as a result of this, we are reminded in hypertrophy of the pharyngeal tonsil of the disturbances of the speech which occur in so-called *adenoid vegetations*. Characteristic of lacunar angina of the pharyngeal tonsil is a peculiar inflammatory swelling of the lateral column of the plica salpingo-pharyngea to which F. Peltesohn¹ has particularly called attention. For an exact investigation of the pharyngeal tonsil a post-rhinoscopic examination is necessary. It is superfluous to mention especially that lacunar inflammation of the pharyngeal tonsil is also due to the same causes which give rise to the disease in the palatine tonsil.

Finally, regarding **angina of the lingual tonsil**, the previously mentioned varieties may also be differentiated. The diagnosis of this condition, which frequently runs its course with diseases of the pharyngeal tonsils, is easy. It is sufficient to depress the tongue somewhat, so that the head of the patient is slightly brought forward. The clinical importance of this affection is slight; cases of peritonsillitis of the lingual tonsil have also been described; they are naturally of more serious import than the affections previously mentioned; however, this affection belongs to the greatest rarities.

THERAPY

In describing the therapy of angina, the general therapeutic precept must be primarily advanced, that the remedial agent must be chosen in proper proportion to the severity of the disease. As catarrhal angina in the majority of cases is a quite harmless affection, it is sufficient to have the patient remain in his room; in a severer affection Priessnitz's poultices are to be applied around the neck, which are to be changed every two to three hours during the day, remaining in place during the night. Each time after removing the bandage the neck is to be thoroughly dried; a gargle is then generally used which should contain some astringent remedy; I am favorable to tinctura ratanhiaë in this form of angina, of which about $\frac{1}{2}$ teaspoonful should be used in a glass of water.

In the lacunar form of angina the fever itself compels the patient to go to bed. It is not necessary to give accurate dietary prescriptions as the swal-

¹ Ueber die Angina lacunaris des Nasenrachenraumes. In Breyer's Sammlung, Bd. v.

lowing of solid food and warm drinks is limited by the pain. As these patients mostly complain of severe pain in deglutition it is advisable to give small pellets of ice, all the more as in this manner an antiphlogistic action is to be hoped for. In some of the drug stores of Berlin ice made from distilled water may be purchased; it would be well if this custom were generally introduced! Besides, it is good practice to use Priessnitz's bandages or ice-bags to the throat; the latter, however, with the express advice that the ice is to be frequently renewed, as, otherwise, it fails in its purpose. If great pain is present, the use of the so-called angina pastilles after Avellis, which now may be purchased of most apothecaries and are made in Neumeier laboratories in Frankfort on the Main, may be used. Of these pastilles, which contain antipyrin and cocain in small amounts, one is allowed to dissolve on the tongue, several times during the course of the day.

Should gargles be employed in lacunar angina? There is scarcely an actual indication for their use as one can hardly believe that by gargling any marked relief may be attained. However, the practice is so universally introduced and frequently it is so pleasant to the patient to rinse his mouth in this manner that for this reason alone a gargle should be ordered. Only, in these cases astringents should not be used. It is also better not to employ potassium chlorate, which is in such general use, as not only in the case of children but also in adults poisoning has been observed after use of this drug. Harmless, and for this reason advisable, is chlorin water, diluted with equal parts of water, or lime-water which is to be used in equal parts in the same manner. Gargles in a luke-warm condition, composed of different kinds of tea, act pleasantly; of these chamomile tea and salbei tea are great favorites. As no result is to be expected from the local application of remedies, surgical treatment of lacunar angina, in the form of extirpation of the diseased tonsil, is not advisable, and a few remarks may be added regarding the use of internal remedies. It is good practice, besides the use of angina pastilles, which have an anodyne action, to use antirheumatic drugs to combat the constitutional symptoms of angina as well as for the prophylactic action for the rheumatic sequelæ of angina. Naturally, any of the antirheumatic remedies may be used, of which such a great number have been introduced in the last few years. Salipyrin (an evening dose of 15 to 20 grains) with a simultaneous use of some sweat-producing tea such as chamomile, sambucus or elder tea is especially valuable.

Regarding the treatment of the deeply situated purulent processes, the remedies may be continued until abscess formation has been determined; however, after pus has formed or even a suspicion exists that pus is present, a sharp knife with a short blade should be used in incising the tonsil, as an abortive treatment is never successful. Even if pus is not found on the first incision, the patient is markedly relieved and the evacuation of pus is rendered easier later on. The incision in the peritonsillar inflammations should be parallel to the border of the anterior palatine arch, directly posterior, and should be several centimetres long. It is good practice to enlarge the incision somewhat with a dull instrument, eventually the blunt end of a knife, so that the pus may flow off readily. As a rule, the pus flows immediately from the incision, if not, pressure upon the neighboring tissues assists this process.

After the difficulties of the patient have been removed, as if by magic, it is well to use gargles, for example, elder tea. The patient should be examined upon the next day and if necessary the incision should be enlarged or dilated as the borders may adhere, thus preventing the rest of the pus from finding an exit.

In the treatment of the exclusively phlegmonous forms of angina, in which abscess does not occur, general directions can hardly be given, as in this disease the appearance of a cellular inflammation of the throat or edema of the glottis are regularly common complications. In general, it is good practice to use ice internally and locally. Views differ regarding operative procedures; in general, a conservative method of treatment is adhered to to-day. The chief aim of the physician, especially in this disease, is to combat an existing or threatening cardiac asthenia in which the recognized remedies (alcohol, camphor, etc.) are to be employed.

Regarding the treatment of inflammations of the pharyngeal and lingual tonsils, no special indications need be given, the treatment being the same as in inflammation of the palatine tonsil.

Two conditions must still be mentioned which are essentially forms of tonsillar inflammation; one of them relates to a free evacuation of the bowels which may be attained by purgatives; this is in keeping with well-founded medical usage whether we act in the sense of the older physicians or not, by attempting to drive off the inflammation by means of the bowel.

Further, in all patients after the disease has run its acute course and especially in those that are more frequently attacked by angina, the use of disinfecting mouth washes is to be recommended; for this purpose potassium permanganate may be used, of which a grain may be used in a glass of water. Miller's mouth water may be advised; it consists of the following:

(a) For permanent use:

Acid. benzoic.....	3.0
Tinct. ratanh.....	15.0
Alcohol. absolut.....	100.0
Ol. menth. pip.....gtt.	xx

Half a teaspoonful in half a wine-glass of water.

(b) For transitory use in inflammatory conditions:

Saccharin.....	2.5
Acid. benzoic.....	3.0
Tinct. ratanh.....	15.0
Alcohol. absolut.....	100.0
Ol. menth. pip.....	1.0

One part in ten parts of water, to be retained in the mouth for one minute.

This point leads us to the discussion of prophylaxis, in which we must differentiate between prophylactic measures for the surroundings of the patient and for the patient himself. For this purpose a small operation is often efficacious which prevents the accumulation of secretion and favors its flow; it consists in the so-called tonsillar incision. With any suitable instrument

—special instruments have been devised for this purpose—the grooves of the tonsils are entered and by the use of slight force the tissues lying between are separated; in many cases this is sufficient to prevent a relapse in angina.

This treatment is often sufficient after the previously mentioned condition, relapsing angina, has arisen, giving rise to hypertrophy of the tonsils especially when the hypertrophy has not reached too great an extent. If incision of the tonsils in these cases has not been successful or if the hypertrophied tonsils give rise to other disturbances, difficulty in respiration, etc., it is advisable to remove the hypertrophied tonsils with the tonsillotome.

Regarding prophylaxis of the surroundings of an angina patient, it has been advised from different points of view to isolate every patient suffering from angina. This can, however, scarcely be carried out, either in the hospital or in private practice. Only in those cases in which the diagnosis between angina and diphtheria cannot be made is it imperative to isolate the infected individual. But even under other circumstances, people that are especially predisposed, particularly children, should be kept away from the patient. Kissing as well as the common use of knives and forks, etc., are to be prohibited.

The physician must always remember that only in a rational therapy is there a possibility of preventing the sequels of angina, and how great a rôle they play has been explicitly described. And if we remember this, we shall certainly agree with Senator when he says: “The older physicians, as is well known, have looked upon the portal vein as the entrance path for so many morbid changes. *Vena portæ, porta malorum*. I believe we might to-day with the same right or probably more correctly designate the vestibulum pharyngis as the ‘*vestibulum malorum*.’”

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MALTA FEVER

By JULIUS L. SALINGER, PHILADELPHIA

MALTA FEVER is a specific, endemic, infectious disease, due to the micrococcus melitensis (Bruce), characterized by an irregular fever of long duration, by arthritic neuralgia and muscular pains, free sweating, constipation, orchitis and an enlargement of the spleen. The mortality is low and the malady is not contagious. Relapses are very common.

The affection is known by a large variety of *synonyms*, relating particularly to the regions in which the disease prevails, such as Mediterranean fever, Neapolitan fever, Danubian fever, Rock fever. Some synonyms also are an attempt to describe some of the characteristics of the malady, thus, gastric remittent and bilious remittent fever, etc. It is also known as undulant fever on account of its wavy, irregular course.

Early writings do not contain descriptions of the disease. Burnett (Practical Account of the Mediterranean Fever, London, 1816) believes this affection to be of a severe remittent malarial character. We owe our knowledge of the disease to Marston, Bruce and Hughes.

There is abundant proof that the affection is by no means limited to Malta. It occurs all along the coasts of the Mediterranean Sea, from Gibraltar to Constantinople; even extending along the shores of the Red Sea. Hislop (Brit. Med. Journal, Sept. 20, 1902) states that the affection is particularly common in India. It is most probably a malady of the tropic and subtropic zones, frequenting the sea-coast and the banks of large rivers, prevailing for the most part during the hotter months of the year. The imported disease has been noted in England and in the United States (Musser and Sailer, Phila. Med. Journal, December 31, 1898). The affection has been noted as occurring on some of the islands of the Gulf of Mexico and in Puerto Rico.

ETIOLOGY

It is particularly a disease of young, robust adults. It appears that insanitary surroundings favor the spread of the disease, although, in regard to the poison, it is not known as yet whether it is air-borne or water-borne. The *exciting cause* of the disease is the micrococcus melitensis, first isolated and studied by Bruce, in 1887. The organism is not found in the blood during the life of the patient. It is present in great numbers in the spleen and by the withdrawal of blood from the spleen (by means of a sterile hypodermic needle) its presence can be demonstrated (Bruce).

BACTERIOLOGY

The organism is oval or rounded and measures $\frac{5}{10}$ of a micron in diameter. It grows singly, in pairs, and sometimes in short chains. It stains with the ordinary anilin dyes and decolorizes by Gram's method.

It is aerobic, nonmotile, and does not liquefy gelatin. It is said to possess flagella. Upon agar slant, colonies will be visible about the third day. As the growth becomes older it changes to a pearly-white color. The organism may be cultivated in bouillon. Growth is not visible upon potato media. The agglutination test has been observed by mixing the serum of patients suffering from Malta fever with the micrococcus melitensis. The agglutinative effect varies in different cases from 1:10 to 1:1,000. Inoculation experiments have been successful in the monkey.

The period of incubation is probably on the average about ten days. It may be longer or shorter than this. It is still undecided as to whether recovery from an attack confers subsequent immunity or not.

PATHOLOGY

The affection is rarely fatal, hence the opportunity for post mortem investigation is limited. The views of various investigators (Perry, Bruce) are still far apart; some claiming to have found the typical lesions of enteric fever, and others stating that no constant typical lesions are present.

The small intestine is usually pale, except the upper portions (the duodenum and first portion of the jejunum) which are most often congested. The mesenteric glands are often enlarged. The spleen is enlarged to a marked extent, the pulp is soft and friable and dark on section. The Malpighian bodies are swollen and indistinct. Cloudy swelling is the principal change in the other organs; the kidneys may show signs of hemorrhage and glomerular nephritis.

SYMPTOMS

The onset of the disease is often characteristic, *prodromes* marking the beginning of the affection. These consist of general malaise, lassitude, dyspepsia, headache, chilliness, epistaxis, etc. In fact, some authorities describe the onset as identical with that of enteric fever. Loss of appetite is common but vomiting is rare. After a few days nausea and vomiting may occur and, in fact, gastric symptoms are more or less prominent until the termination of the affection. The bowels are constipated but there may be diarrhea. The patient is chilly and feverish and notes that his condition is aggravated from day to day.

In more marked cases, the headache is intense, it is often frontal in position and there is early enlargement and tenderness of the spleen. Restlessness and insomnia are common and the apathy of the patient is often extreme. After a variable period, of a few days to a week or more, these symptoms decline and the patient believes that he has recovered, but very soon (after two or three days) a relapse occurs, all symptoms returning, and even stools of a dysenteric character being noted. With this there is marked

muscular pain and decided anemia. The stools are dark colored and do not resemble the "pea-soup stools" of enteric fever.

In the severer cases, nervous symptoms are prominent. Stupor with low muttering delirium may appear, in fact, all the symptoms of the "typhoid state" may be present. To this there may be added pulmonary congestion and even inflammation of the lungs. Epistaxis and hemoptysis are not rare and in these cases marked arthritic involvement, pains and effusions into the joints are present. Some complication (endocarditis) may terminate life.

Temperature.—The temperature curve is characterized by its marked *irregularity*, no one type of fever being constant. Remission, intermission, followed by a subcontinuous course, alternate. In general it may be said that the fever ranges between 101° F. and 104° F. The early morning may show subnormal temperatures. In fatal cases hyperpyrexia occurs.

Digestive System.—The tongue is coated and shows a red tip. This coating remains during the entire course of the affection. Aphthous stomatitis is common. The appetite is variable. Constipation is the rule, but there are many exceptions. Vomiting often occurs late in the attack, it is uncommon as an early symptom. The spleen is enlarged and tender to palpation. Sometimes enlargement of the liver may be noted.

Circulatory System.—The pulse is not markedly increased, rarely reaching 100 per minute, except late in the disease. Hemic murmurs occur, but they are most likely due to the anemia which occurs in the disease. The erythrocytes are decreased in number and the hemoglobin is diminished. Epistaxis, hemoptysis and purpura are noted.

Respiratory System.—Bronchitis is common. Pneumonia and pleurisy are complications which occur late in the disease.

Genito-Urinary System.—Orchitis and neuralgia of the testicle have been noted in quite a number of cases. The daily amount of urine is slightly decreased, in cases with high and prolonged fever albumin is present. The urine then shows the usual characteristics of "febrile urine." Sometimes the superficial lymphatics are enlarged and may even suppurate.

Nervous System.—Headache is common and may be very severe. The face is pale and shows the general anemia of the patient. Delirium is limited to the severe cases. Neuralgia and neuritis are quite common conditions.

Skin and Joints.—Various forms of eruption are noted, such as erythema, erythema nodosum and eczema. In cases with marked sweating, sudamina occur. Alopecia is present in almost every case.

The joints are commonly tender and often swollen. The hip joint is the most common one to be involved, although any of the other articulations, even the small joints, are by no means spared. Effusions may even occur in the joints.

DIAGNOSIS

In regions in which Malta fever is endemic the diagnosis, as a rule, presents no difficulties. In imported cases, however, the diagnosis gives rise to much uncertainty. The direct diagnosis depends upon the age of the patient, the atypical temperature, the headache, the peculiar pains in the joints, the gastric symptoms, the relapses and the agglutination test. Withdrawing

blood from the spleen in the attempt to demonstrate the micrococcus melitensis is always a questionable procedure. If attempted at all, it must be carried out with the strictest antiseptic precautions.

DIFFERENTIAL DIAGNOSIS

From a differentio-diagnostic standpoint, the following affections bear some resemblance to Malta fever: Enteric fever, dengue, malaria, and acute rheumatic fever.

The differential diagnosis from *enteric fever* can be made by the presence of the Widal reaction, the typical temperature, the eruption, the dicrotic pulse, the presence of possible complications (intestinal hemorrhage, perforation), the prominence of the nervous symptoms in enteric fever.

Dengue should not present differential difficulties, as the affection begins suddenly, the fever lasts about three days and the pains in the joints are prominent from the onset, whereas in Malta fever the arthritic and muscular pains occur late in the disease, however, in doubtful cases the agglutination test is final.

Malaria reveals the presence of the plasmodium and even when the protozoa cannot be detected at once the course of the temperature is different, as a rule, higher temperatures being found in malaria than in Malta fever, and the arthritic pains are not so prominent. However, it must not be forgotten that forms of so-called "masked malaria" present themselves as typical neuralgias.

Acute rheumatic fever shows joint involvement from the onset. The arthritic involvement is of a fleeting character, symmetrical joints being involved. Cardiac complications are common, whereas in Malta fever these intercurrent valvular affections are exceedingly rare.

PROGNOSIS

The mortality is very low, according to Bruce it is about 2 per cent. Continued high temperatures, pneumonia and endocarditis render the prognosis serious.

TREATMENT

The chief indication of the treatment consists in careful nursing. The diet should consist of nutritious food, in small quantities, but frequently administered. Milk, beef tea, and chicken broth are best for this purpose. Water in liberal amounts is useful. Where liquid food is rejected semi-solid food is often retained.

Alcohol as a routine treatment is not necessary, only being indicated in those cases that are characterized by decided cardiac asthenia and anemia or in cases in which complications, such as a low grade of pneumonia, develop. Where a cold bath is given to relieve excessive temperature the administration of a small quantity of whiskey before and after the bath is of use.

It is well to begin the treatment by the administration of a laxative; broken doses of calomel or castor oil may be administered. This should not

be repeated for it must always be remembered that there is a tendency to diarrhea in this affection. Mild cases require no other drug treatment.

In the severer cases, in which headache and muscular pains are marked, the cautious administration of antipyrin has been found of great value. It reduces temperature, relieves the pain and often controls the restlessness so that sleep is produced. If this drug is not sufficient to control the pain, opium in some form must be resorted to. The salicylates are not effective. If the diarrhea becomes a prominent symptom opium is the most reliable remedy. For prolonged high temperature or hyperpyrexia the cold bath (68° F.) has been found most efficient. Complications must be treated upon general principles.

In convalescence it is well to remove the patient to some temperate climate. Experience has shown that patients recover but very slowly if they remain in tropical or subtropical countries, in which the disease is endemic. During convalescence it is necessary to control the anemia by the use of iron in some form and by nutritious diet.

WEIL'S DISEASE, ICTERUS INFECTIOSUS, ACUTE FEBRILE ICTERUS

By J. C. WILSON, PHILADELPHIA

WEIL, in 1886, described an acute infectious disease characterized by sudden onset with chill followed by high fever and later jaundice. Clinicians are not in accord as to whether or not the affection referred to is to be regarded as a definite nosological entity or merely one of several acute febrile infectious processes accompanied by jaundice. The clinical picture suggests the severer cases of catarrhal jaundice and various febrile forms of gastrointestinal disease that may run their course with or without jaundice. It corresponds very closely to the infectious disease observed by Griesinger in Cairo and Kartulis in Alexandria, and described under the designation bilious typhoid or typhus biliosus. The literature abounds in cases reported as Weil's disease which clearly do not belong to that category, such as santonin poisoning, septicemia, abortive enteric fever, and the so-called hepatic form of enteric fever. The view that Weil's disease is a form of rheumatic fever complicated by a resorption icterus (Leiberlinger) is not generally accepted.

Certain etiological considerations tend to support the assumption that the disease is the manifestation of a specific infectious process. Among these are the following facts:

The cases which correspond to Weil's description frequently occur sporadically, but not rarely they appear in groups in circumscribed localities, and during the hot season. Males are more frequently affected than females—90 per cent. Certain occupations exert a predisposing influence, butchers, tanners and laborers in sewers being especially liable to the disease. It has been attributed to the drinking of contaminated water, and epidemics, especially among soldiers, have been ascribed to the swallowing of such water during bathing. The disease is most frequent between the twenty-fifth and the fortieth years of life. It is uncommon in childhood, and rare after fifty. The number of cases reported in America is limited.

The researches of Jäger render it probable that an organism cultivated from the urine of living cases and from the organs of a case dead of the disease—*proteus fluorescens*—is the infecting agent. These observations have been confirmed by subsequent investigations.

SYMPTOMATOLOGY

The attack begins abruptly, usually without prodromes and often with a chill. Headache, vertigo, pain in the back and limbs occur. There is great lassitude. The temperature rises rapidly to 104° F. (40° C.) or higher and

its range conforms to the remittent type. It lasts from eight to fourteen days. There are recurrences of the fever, and in a considerable proportion of the cases relapses occur. The tongue is coated, the spleen enlarged and diarrhea is not uncommon. Stupor and delirium occur, and the resemblance of some of the cases to enteric fever is striking. This resemblance is increased by the early development of splenic enlargement. Jaundice appears between the third and the fifth days and varies in intensity, being in many of the cases deep and attended by clay-colored stools. The liver is increased in size and is tender. The urine is commonly albuminous with hyaline and epithelial casts and sometimes red blood-corpuscles. Hematuria is not very uncommon. In the fatal cases deep stupor, delirium and coma occur. There is rapid wasting during the attack. The muscular pains persist after the defervescence and are among the last symptoms to disappear. Angina tonsillaris is an occasional early complication. Herpes facialis and other cutaneous lesions, as erythema and hemorrhage into the skin have been noted. A group of the graver cases are hemorrhagic, being characterized not only by cutaneous hemorrhage but also by epistaxis, subconjunctival hemorrhage, and blood in the stools, urine and expectoration. Parotid bubo is a rare complication. The duration of the attack varies from two to four weeks and the convalescence is tardy.

The mortality is low, most of the cases terminating in recovery. The post mortem findings are not characteristic. They show recent enlargement of the spleen, which is soft and vascular, and of the liver, the cells of which show cloudy swelling. The kidneys are enlarged and congested showing parenchymatous changes.

DIAGNOSIS

The direct diagnosis rests upon the occurrence of jaundice with the symptoms of an acute severe infection quite unlike ordinary catarrhal icterus on the one hand and without the phenomena of the specific infections on the other. The age, sex and occupation of the patient are to be considered. It is probable that some of the local epidemics reported as catarrhal jaundice of severe type have been outbreaks of Weil's disease.

TREATMENT

The treatment is expectant-symptomatic. The early administration of calomel followed by a saline is, notwithstanding the tendency to diarrhea, to be advised. A light diet and water in abundance are indicated. The high temperature demands cold sponging, the cool bath or cold packs. Hypodermoclysis and enteroclysis have been employed with benefit.

TETANUS

By P. JACOB, BERLIN

THE affection about to be described, belongs to the group of those, which fortunately, due to the development of medical science in the last two decades, has been completely revolutionized. Although for many centuries the symptom-complex of the individual forms of tetanus have been more or less well known to physicians, the actual cause of its development has only been known for a few years. The knowledge of the nature of this disease and the methods of combating it, in comparison with former times, have changed so completely that we are almost justified in looking upon tetanus as a new affection. Only in one other infectious disease besides tetanus, in diphtheria, have the investigations in the bacteriologic, chemical, microscopic, pathologic and clinical fields shown such great results; in all the other infectious diseases, either we do not know the pathogenic agent at all and have no specific therapy (scarlatina, measles, syphilis) or the pathogenic agent is known but no specific remedy has been found as yet (tuberculosis) or finally, empirically, a specific protective substance has been discovered, also the pathogenic agent of the disease being known (smallpox). Only in the case of diphtheria and tetanus have we succeeded in discovering the bacteria which produce the disease and in recognizing their characteristic properties minutely, also in discovering the specific curative agents, the antitoxins. Thus, we may look upon both diseases simultaneously as a prototype for the investigation of all other infectious diseases.

As already mentioned the symptoms were known to the ancients. The master of ancient medicine, Hippocrates, has given an excellent description of them; in the works and writings of numerous other authors of antiquity, as well as in those of the last century there are many theses and observations of tetanus in man which are well worth reading. In these writings, on the one hand, the attempt is made to describe the clinical symptoms of the disease as accurately as possible; on the other hand, it may be noted that the actual nature of the disease was entirely unknown in the endeavors to differentiate distinct forms of tetanus: according to age and sex of those attacked by tetanus and according to the individual regions of the body, which showed the characteristic phenomena produced by the disease. The causes which might give rise to tetanus have also been previously investigated upon many occasions; long before the actual pathogenic agent was discovered many physicians held the view that tetanus occurred particularly in connection with injuries. It was known that many soldiers in battle did not succumb to their actual wounds but to tetanus which was the result of them; often the obser-

vation had been made that tetanic symptoms showed themselves especially if the wound was contaminated. Not rarely was it observed, especially in the pre-antiseptic period, that tetanus occurred in connection with surgical operations and with the puerperal state. It was also believed that occasionally other influences, not exclusively traumatic ones, thus refrigerations, etc., might develop tetanus. But even in the middle of the previous century, the view became more and more prominent, that tetanus was an infectious disease; and the proofs of this were adduced two decades ago. Early in the eighties of the last century two Italian authors, Carle and Rattone, succeeded in producing tetanus experimentally in rabbits that they had injected with fluid obtained from a pustule in a case of tetanus. In the year 1884 the true cause of tetanus, the tetanus bacillus, was discovered by Nicolaier in garden earth; since this important discovery, a new epoch has begun in the investigations and knowledge of tetanus.

It appears wise to briefly consider at this point the results of the labors connected with the discovery of the tetanus bacillus in the last fifteen years, in a bacteriologic, etiological, chemical and anatomico-physiological respect. I shall not enter into minute details, nor shall I discuss points which are still doubtful, but it is necessary that the nature of the tetanus bacillus and the action which it produces in the animal organism must be known to the physician, so that he will be able to appreciate the practical consequences.

THE TETANUS BACILLUS

Regarding the microscopic properties of the tetanus bacillus, the bacillus discovered by Nicolaier presents a slender straight rod, the end consisting of a button-like thickening which is to be looked upon as a spore. The tetanus bacillus carrying a spore has been compared to a pin [or a drumstick]. Deviating from this original form, which Nicolaier found in garden earth spores were also found, in which this button-like thickening was not found, which represent slender straight rods with rounded ends.

After the discovery by Nicolaier, the observations of authors increased and it was proven that this specific bacillus was found in immense numbers in nature; not only in the open, in garden earth, in dust of the streets, could it be demonstrated, it was also found in dwellings, upon floors, in furniture, in drawers and in stables, and even in the feces of horses and occasionally in the feces of human beings could it be cultivated. Its occurrence in nature does not appear to be everywhere uniform. Great variations are noted in this respect in Europe; whereas the tetanus bacillus, for example, cannot be frequently found in Berlin, in Prague its presence could be demonstrated upon numerous occasions; it appears to be particularly frequent in the tropics or at least in individual tropical countries. In connection with this is the experience that tetanus bacilli have been demonstrated in the arrows of savages; to this circumstance perhaps may be ascribed the murderous action which so frequently takes place in wounds due to such arrows.

In spite of the fact that tetanus bacilli occur so frequently in nature, and although the opportunity is frequent enough for infection to take place—for the smallest wound is sufficient to serve the tetanus bacillus as the point of

entrance—the total number of infections cannot be said to be very great. The reason for this is found in the *biologico-chemical properties of the bacillus*.

These have been the subject of the most careful study during the last few years. To determine the conditions by which it is possible for the tetanus bacillus to enter the smallest wound and within a few days produce such a destructive action, which for the most part causes death, the attempt was made, on the one hand, to develop the products of metabolism of the bacillus and to study their action in the animal organism; on the other hand, the chemical and microscopical changes which occurred in the fluids themselves of the organism after the entrance of the tetanus bacillus into the body was accurately investigated.

Three conditions are required by bacteriology, in general, to determine the specificity of a pathogenic agent; first the presence of the same in one or a species of animals (including man); secondly, the culture of the bacterium in cultures; and thirdly, its transmissibility from one living organism to another. By Nicolaier's animal experiments success was only attained in the last proof. Nicolaier was able, by injection of the bacillus that he found in garden earth into mice, guinea-pigs and rabbits, to produce typical tetanic phenomena in these animals. In connection with these injections pus foci develop at the point of injection; in these Nicolaier also found bacilli and by inoculating other animals with these he was able to produce tetanus. However, he was not able to demonstrate these bacilli in man, nor to produce pure cultures with them. The first proof was attained a short time afterward by Rosenbach following Nicolaier's publication. The last proof was demonstrated some few years later by the well-known Japanese investigator Kitasato. In the year 1889 he isolated from a wound of a man suffering from tetanus the typical tetanus bacilli, and he produced pure cultures by a process which depended, in the main, upon keeping the culture media *completely free from oxygen*.

Now only were we enabled to enter somewhat more minutely into the characteristic nature of these bacilli and many problems have been solved by experimenters in this connection. The first investigators had already noted that tetanus bacilli only flourish at their point of entrance into the organism, i. e., that they do not enter other organs, nor are carried into them. But a few authors did not coincide with this view; and in these cases a mixed infection was probably present, which permitted the tetanus bacillus to exist in other areas of the organism simultaneously with other bacteria than at its point of entrance. In general the opinion was almost unanimous that the tetanus bacillus had but a very short life in the wound, i. e., at its point of entrance. Frequently at the height of the disease it can no longer be discovered in the wound. This probably explains why so many investigators, searching for years, were not able to discover the cause of tetanus. Further, cultivation of the bacillus could only succeed after its peculiar properties of growth upon culture media were more closely investigated. The tetanus bacillus only grows anaërobically; Kitasato recognized this peculiarity in the production of his culture media in attempting to procure pure cultures of the bacillus. Among the properties of the tetanus bacillus there is still to be recognized that it belongs to the most resistant bacteria known to us at present. It is extraordi-

narly resistant to external influences (heat and chemical agencies, etc.) and it is capable of retaining its complete virulence for years in dust, in water, and on substances upon which it has dried.

Thus in the year 1890 by means of bacteriologic investigation the pathologic agent of tetanus was known and recognized everywhere. Soon, however, the opinions increased of authors who maintained that the bacillus as such did not produce the severe phenomena which so frequently cause death, but that these conditions were due to *products of metabolism* which should be ascribed to the influence of the bacillus.

Bacteriologic chemists now busied themselves with an examination of the nature of these toxins and although these investigations have not as yet been definitely concluded they have at least had the result that we are able to experiment with the toxin produced from the tetanus bacillus in animals and thus are enabled to minutely study the nature of the affection. Among the authors who have investigated the "chemistry of tetanus" are Brieger and his pupils, Kitasato, Wassermann, Blumenthal, Weyl, Roux and Yersin, Tizzoni and Cattani, Uschinsky, Buchner, Behring, and, above all, Ehrlich.

Gradually a toxin was isolated from the bacillus which, even with an extraordinary dilution, was able to produce death in the animals experimented upon, giving rise to the characteristic phenomena of the disease. The substance which is utilized in animal experiments does not represent the actual, pure chemical toxin; but it comes very close to it; its toxicity is so great that the millionth part is sufficient to cause death in mice.

Not all species of animals are alike susceptible to the toxin of tetanus, according to a compilation given by v. Leyden and Blumenthal. In a monograph which has recently appeared the most susceptible species of animals are: the horse, the goat, man, the ape and the guinea-pig, then mice, donkeys, mules and cows; rabbits, dogs, rats, cats, pigeons, and crows are less susceptible. Chickens are only susceptible to extraordinarily large doses. The following triton varieties have been found to be non-susceptible: turtles, scorpions, lizards, as well as parrots and aquatic birds. (The following descriptions naturally only refer to those varieties of animals which are more or less susceptible to the tetanus toxin.)

A further stage in the investigation of tetanus was reached—after it was possible to obtain the tetanus toxin from the tetanus bacillus in a comparatively pure condition—in regard to the distribution of the tetanus toxin in the animal organism. For this purpose the organs of animals were analyzed in whom tetanus bacilli or the toxin were injected, secondly the organs of human beings that had died of tetanus, in whom therefore the bacilli had entered through a wound into the body.

It was soon shown that, in contrast to the property of tetanus bacilli to only live at the point of entrance, the toxin developed by them enters the body with extraordinary rapidity. Upon culture media, inside of a few days it forms in quite large amounts and can be obtained readily from the filtrate. This toxin then produces the clinical symptoms of tetanus, points which were particularly developed by the labors of the French school. The correctness of this theory is shown by the following tests: If an animal is injected with a

large amount of bacilli, which have been deprived of their toxicity, it is never possible to produce morbid phenomena. In explanation of this conspicuous behavior of the bacilli, the phagocyte law has been invoked. It is assumed that if bacilli that have entered the organism do not produce sufficient toxin at their point of entrance, an accumulation of white blood corpuscles occurs in the wound, a positive chemotaxis occurring, and that the leucocytes which have recently accumulated in the wound destroy the spores of the bacilli which produce the toxins. If, on the other hand, the bacilli, after their entrance into the wound, very soon cause the production of toxins this is a negative chemotaxis, the white blood corpuscles are dissipated, the spores are not destroyed, the toxin which is formed enters the circulation and the organism.

Two varieties of alterations are produced by this action, first a *purely chemical one*, and secondly, *changes in the cells*. We shall first consider the former.

Up to a few years ago we were not able to ascertain in which organs the principal amount of toxin is present which is produced by the tetanus bacilli. The symptoms at the height of the disease were almost inexplicable. In the wound itself during this stage the bacilli were not present at all or could only be demonstrated in slight amounts and in the blood only traces of the toxin could be found. Cases were observed in which persons perished with severe symptoms of tetanus, without their blood which was inoculated into mice producing morbid phenomena. Where then is the principal amount of the toxin found in this period which gives rise to the affection?

Recent investigations from Behring's laboratory prove—at least after a subcutaneous injection of the tetanus toxin in animals—that it first enters the lymph channels and then only the circulation, therefore is not directly taken up by the capillaries of the blood. After it has reached the circulation it remains in the blood in varying quantity for a longer or shorter period. In this respect different species of animals show great variation among each other: In one animal a few hours after the injection of the toxin, only traces can be demonstrated in the blood, in others often the entire amount of toxin may be found in the circulation even after one or two days. In general, however—the investigators are unanimous in this—at the height of the disease the amount of toxins circulating in the blood is not so considerable that the severe symptoms of tetanus could be satisfactorily explained from their presence.

In the other fluids of the body, the toxin of tetanus at the height of the tetanic symptoms is not found at all, or in very varying quantities. In the cerebrospinal fluid, only two investigators up to this time have succeeded in demonstrating it, each in one case; first Stintzing, and lately Blumenthal (in a case treated by subdural injection in the First Medical Clinic in Berlin).

The urine, at least in human beings who have been attacked by tetanus, never contains toxins according to the investigation of all authors; only in tetanus experimentally produced has it been discovered in the urine in a few cases.

Regarding the internal organs of the thorax and abdomen, during the

period of the appearance of the tetanic phenomena in general, great amounts of toxin have never been found, so that the point of deposit of the toxin cannot be in these localities. Various investigators succeeded in finding the toxin in nearly all the organs of animals in which tetanus had been experimentally produced.

Thus there is only one set of organs in the body in which a special connection with the tetanus poison could be assumed: the *central nervous system* (eventually including the peripheral nerves).

Common sense postulated—if we may be permitted to use this expression, one applied by Johannes Müller upon another occasion—a certain connection between the general tetanic symptoms and the especial implication of the central nervous system: A large part of the symptoms cannot be otherwise explained than that they are due to a disease of the nervous substance. For a long time before the scientific investigation of this complicated disease was attempted and without there being any other than a clinical basis for it, physicians and clinicians pointed to the importance of the central nervous system in tetanus; some clinicians, for example, R. Romberg, went so far that they designated tetanus directly as a reflex neurosis, including it among the spasms, the point of origin of which they referred to the spinal cord. Other authors believed that not so much the spinal cord, as the cerebrum was the centre of this tetanic disease, and still others referred the main seat of the affection to the peripheral nerves—briefly, the investigators who busied themselves with the discovery of the tetanus bacillus and with the determination of its specific properties, had their line of investigation prescribed for them by their medical ancestors.

After laborious work, but in a brilliant manner, success has been attained in the last few years in determining the scientific basis for this view, *that the affinity of the tetanus toxin for the substance of the central nervous system which was formerly only presumed, exists to a high degree.* On the one hand, the animal experiment was decisive; in the nervous substance of man who had perished from tetanus, as well as in that of animals after artificial infection, when killed or perishing from the affection, numerous investigators succeeded in demonstrating the toxin in decided amounts. Further, it was shown that the nerve substance extirpated from the bodies of healthy animals showed especial attraction for the tetanus toxin. Although it is my intention to speak of antitoxin therapy only at the end of this article, nevertheless at this place some results of investigation must be mentioned which relate to these questions. By experiments made by Wassermann and Takaki, by Blumenthal and some of his pupils, further by Metschnikoff, and individual French investigators, especially, however, by Ehrlich, as well also by some other authors, it was shown that the substance of the central nervous system of certain animals contains products which have a very peculiar affinity for the tetanus toxin. For several years scientific discussion undulated to and fro, considering the activity of these substances; while some believe that they were only substances which combined with the toxin produced by the bacteria, others believed these substances a pre-formed antitoxin of the nerve-cells which was capable of paralyzing the toxic effect of the bacteria.

This dispute even to-day is by no means completely settled; however, the

theory proposed by Ehrlich shows so much that is logical and rational that I incline to this view in explaining the importance which the substance of the central nervous system has in giving rise to the symptoms of tetanus. If I may be permitted to alter a few designations, so that I may be able to explain *Ehrlich's theory* in a simple manner, this is all that shall be attempted by me.

I should like to designate the peculiar substance which is found in the central nervous system of all animals that are susceptible to tetanus by the collective term "*tetanoid substance*." I propose this name for the reason that this substance, as taught by Ehrlich, must fulfil various functions and outside of the designation "*tetanoid substance*" special attributes must be attributed to it, to obviate confusion, which is frequently due to an incomplete terminology.

As already mentioned, the tetanoid substance is present in the central nervous system, before animals (including man) are attacked by tetanus: that is it is *pre-formed*. Its first function consists in this, that after the bacilli have accumulated in a wound and the toxin produced by them has entered the circulation, they attract the toxin enchaining or combining with it; therefore, this pre-formed tetanoid substance has also been called "*toxin combining*" substance, or, according to Ehrlich, it has been designated as the *haptophorous group*. *The actual disease, tetanus, depends upon this toxin combination; so long as new toxins are attracted by the nerve-cells so long as toxin-forming substances are present in them and, finally, the latter pair (or as the condition has also been expressed it enchains with these), so long the disease with its characteristic symptoms remains prominent and terminates lethally under all circumstances, provided the enchaining process occurs in vital nerve-centres.*

But this enchaining of toxin is not the only function which the nerve cells must fulfil. Besides the pre-formed tetanoid substance the cells, after they have thrown off the first haptophorous groups, which have been paired with the toxin, into the circulation, execute another function—according to a biologic theory which Weigert has ingeniously proposed—while the morbid process constantly produces new amounts of tetanoid substance, new haptophorous groups form. *In contrast to the PRE-formed substance, I should like to designate this as the "POST-formed tetanoid substance."*

How much of this post-formed tetanoid substance the toxin chaining in the central nervous system must complete depends on varied conditions under which the affection runs its course, upon the amount of toxin produced from the bacteria, upon the post- and pre-formed tetanoid substance, etc. *It is quite evident that at a certain stage of the disease a portion of this post-formed tetanoid substance is excreted by the nerve cells and thus reaches the circulation. This portion of the tetanoid substance, Ehrlich believes to be the natural antitoxin produced by the organism itself; it takes up the toxin which is newly formed by the bacteria in the circulation, paralyzes it and thus prevents it from pairing with the toxin-binding substance in the central nervous system.*

It is this toxin which, as we shall see later on, has been produced in an experimental manner in animals and then utilized for immunization and

curative purposes. At this point I should like to mention a few facts which, although they are as yet not important in practice nevertheless in a scientific respect are of great interest. On the one hand, experiment has shown that animals susceptible to tetanus are also capable of furnishing active tetanus antitoxin if, instead of injecting the toxin, a modified tetanus virus is introduced, which does not give rise to tetanus (Ehrlich's toxoids). Secondly, it has been shown that also in the blood of animals that are not at all susceptible or only to a slight degree, for example, chickens, crocodiles, etc., antitoxin may be obtained if tetanus toxin is injected a few days previously; these animals, therefore, furnish the specific antitoxin without the toxin injected giving rise to any symptoms of the disease. A third interesting fact is this, that if animals that have had tetanus toxin injected and which already have large amounts of tetanus antitoxin in their blood, during this period have injected only a small, otherwise by no means fatal dose, these animals rapidly succumb to tetanus. The fact first demonstrated by Courmont and Doyon afterward confirmed by Halsey and Hans Meyer is very peculiar, that the body heat has a decided influence upon tetanic intoxication (at least in the animal experiment). Animals kept at a cool temperature are only attacked many days later by tetanus when injected with a 30-700 times fatal dose. A satisfactory explanation of this very remarkable fact obtained by experiment cannot as yet be given. In general these facts are all capable of being explained by Ehrlich's theory, excepting the last.

Most authors, among them myself, in general favor this view. Only the slight limitation mentioned above must be made in my opinion in the interest of a more general comprehension of the process: at least in terminology, the *pre*-formed tetanoid substance should not be identified with the toxin-chaining *post*-formed substance; for although both substances are chemically identical, yet their functions are very different. The division into *pre*-formed and *post*-formed tetanoid substance is not meant to indicate that a large portion of the *post*-formed tetanoid substance, that is the antitoxin, may not remain for a longer time in the nerve cells before it reaches the circulation; if this view were not accepted the opinions of those authors could not be explained who were able to protect other animals from a many times fatal dose with the extract of nerve substance of animals that had succumbed to tetanus. On the other hand, the process of toxin-chaining between the toxin excreted by the bacteria and the *pre*-formed (partly perhaps also of the *post*-formed) tetanoid substance, therefore the process which causes the disease, may so completely overpower the process of repair in the circulation that the secretion of the *post*-formed tetanoid substance (the antitoxin), although the antitoxin is positively present in the central nervous system and under some circumstances also in the circulation, may, nevertheless, cause the animal to perish.

The fact that in one and the same disease an organ may carry on several functions also finds its analogy in other infectious diseases. In this respect, enteric fever may be considered. Here, as newer investigations have taught, the spleen during the febrile course of the disease performs the function of chaining the toxins. Whether the result of this combining of the typhoid toxin and that contained in the spleen, or that formed in the spleen which

chains toxins gives rise to an antityphoid toxin is a problem that has not yet been solved. This much is, however, certain, that the spleen during the time of toxin chaining of the typhoid toxin does not at all or only to a very limited extent perform its hematopoietic function; as a result of this, we find in contrast to almost all other febrile infectious diseases, in uncomplicated enteric fever, that a hyperleukocytosis never occurs.

A further proof that a substance is pre-formed in the central nervous system of animals susceptible to tetanus which is closely related to tetanus toxin was furnished by ingenious experiments of various authors. If the substance of the brain and spinal cord of such animals is rubbed up with a physiological salt solution and to this mixture a certain amount of tetanus toxin is added and now a mixture of an otherwise fatal dose of tetanus toxin is injected into trial animals, symptoms of the disease do not appear in them. By a mixture of the cerebral and spinal cord substances, and of the tetanus toxin, a sufficient quantity of material must have formed which is identical with that produced in the living animal body, the post-formed tetanoid substance; that it is capable of arresting the tetanus toxin which is injected into the experimental animal, to neutralize it and prevent its enchaining with the pre-formed toxic-chaining substance. Further, Ehrlich's theory gives an explanation for this, that if a mixture of the substance of the central nervous system which does not contain tetanus toxin is injected into animals, this is no longer capable of protecting the animals from a later resulting tetanus affection; on the contrary, it is to be presumed *a priori* that under such circumstances, the infection in the animals experimented upon must run a severer course than if they have been previously injected with a mixture of the brain and spinal cord substance; for the toxin produced by the bacteria in addition to pairing itself with the normally present pre-tetanoid substance also finds a toxin-combining substance in the circulation: the mixture injected from the tetanus infection. If the attempt is to be made to immunize animals, or man, against tetanus infection by the process of brain-mixture injection this mixture must first have added to it tetanus toxin prepared outside of the animal body, the post-formed tetanoid substance must be produced by this outside of the animal body and this preparation injected into animals that are to be protected.

Among other arguments which show the affinity of the central nervous system for the tetanus toxin we must mention the results of *subdural injection* of the toxin and of the microscopic investigation of the spinal cord. Regarding the former, the method of use will be mentioned in the therapy of tetanus; here we shall only say that if tetanus toxin is injected into animals into the subarachnoid space, the first symptoms of the affection are noted after from twelve to sixteen hours, whereas if the same dose is injected subcutaneously the period of incubation lasts from three to four days. These experiments were carried out by Blumenthal and myself in the winter of 1898 and 99; lately they have been repeated by Gumprecht and later also by Ransom; both authors arrived at about the same conclusions. Ransom's investigations complement those of Wassermann and Takaki which were previously mentioned. He was able to demonstrate the intimate affinity of the central nervous system for the tetanus toxin which Wassermann and Takaki also proved

in experiments in test tubes and also in the living animal body. Lately Ransom and Hans Meyer found experimentally that if the spinal cord itself is inoculated with tetanus toxin the period of incubation is extraordinarily shortened. These experiments prove in themselves, the theory previously proposed by other authors, that tetanus arises from central causes with the exclusion of every peripheral affection. Regarding the development of tetanus in man, this mode of infection need not be considered as the toxin distributes itself from the point of entrance of the bacilli. Ransom and Meyer believe it probable, upon the basis of their experiments, that the tetanus toxin from the point of infection principally reaches the ganglions of the central nervous system by means of the peripheral nerves; other authors maintain that the tetanus toxin is transported to the spinal cord by the blood and lymph channels. These questions require further elucidation, without, however, affecting the law of the affinity of the central nervous system for the toxin of tetanus.

The proof of the close relation existing between the cells of the central nervous system and the tetanus toxin can be demonstrated with less exactness by *microscopic investigation* than by chemistry. Various investigators among them, above all, Goldscheider, and Flatau, further Beck, Nissl and others found changes in the ganglion cells, during the period of latency in tetanus as well as in the further course of the affection; these cell alterations however, occur on the one hand, to a like extent and in the same manner—they are principally swelling, later shrinkage of the cells and alterations of the chromatin flakes, which may be determined by the method proposed by Nissl—in other experimentally produced intoxications (after strychnin, eel poison injections), on the other hand, they are found in man perishing from various febrile diseases. Finally, there must be mentioned, as was shown by Goldscheider and his pupils, that not the slightest congruent relation can be noted between the severity of the tetanoid symptoms and the degree of the anatomic cell alteration. *We must, therefore, search for the nature of the symptoms caused by tetanus in the central nervous system, more in a specific chemical change of the nervous substance than in a microscopic cell alteration.*

After this law had been enunciated upon the basis of scientific investigation, a further question was propounded, whether the other parts of the nervous system showed the same great affinity for the tetanus toxin or whether differences could be determined. Primarily it was noted that cerebral disturbances, very frequently in the course of tetanus, do not occur at all; doubts began to arise whether a pre-formed tetanoid substance was present in the brain at all, but this question was finally affirmatively settled by two sets of experiments. On the one hand, Wassermann by his experiments determined the presence of the tetanoid substance in the cerebrum, on the other hand, Roux and Borrel, in injecting tetanus toxin directly into the cerebrum of a guinea-pig and a rabbit, were able to determine the specific action of the toxin upon the brain. The question, why tetanus toxin in man, in spite of the tetanoid substance in the cerebrum, so rarely gives rise to tetanoid symptoms cannot be decided at present differently than that the individual portions of the central nervous system vary in their susceptibility to the toxin:

One part is affected before the others. By this explanation, the fact can best be understood that the spasms, we might almost say, arise paroxysmally, corresponding to the individual regions of the spinal cord; we shall refer to this again later on, in the description of the clinical symptom-complex.

Finally, we must still settle the question, *which regions of the spinal cord are in closest relation to tetanus*, i. e., whether the spasms, etc., due to disease of the spinal cord are to be referred more to the motor or to the sensory neuron. In this respect experiments have been carried on by numerous investigators. The individual ones need not be described, but only the results will be reported: According to these results it may be concluded that the tetanus toxin does not exert an independent action upon the peripheral nerves, nor upon the peripheral motor nerve fibre, upon its end twigs nor finally upon the muscle fibre. Neither is the sensory neuron damaged by the tetanus toxin to the extent that this alone would furnish an explanation for the exceedingly severe spasmodic phenomena.

Although the part played by the sensory neuron, in the course of tetanus, must by no means be depreciated, still greater importance must be attached to the motor neuron in the origin and further development of the tetanic phenomena. And thus we cannot close this chapter better than with the words that Leyden and Blumenthal have placed at the close of their chapter "Regarding the pathology of the contractions of tetanus": "*The main action of tetanus toxin represents an increase of the irritability of the motor centres of the spinal cord and of the medulla oblongata.*"

SYMPTOMATOLOGY

After having attempted to familiarize the reader with the mode of life of the infectious agent of tetanus and its action in the human and animal organism, I shall now describe the terrible phenomena which the bacillus causes in man; this constituting the *symptomatology*. Before doing this, however, I must describe the division of tetanus into its various forms. Although, as has already been mentioned, we recognize but one etiologic factor for all forms of tetanus, the tetanus bacillus, and also those cases in which it is not possible to recognize the point of entrance of the bacillus are not accepted, it is still advisable for clinical purposes to make some differences by terminology. There are three ways, above all, in which the tetanus bacillus enters the organism: 1. From the skin after a general injury of greater or less severity (fissures upon the hands or feet, wounds acquired in war, severe injuries to the soft parts, etc.); 2. By way of the genital tract of women (especially during or a short time after abortion, or after labor); 3. By means of the umbilical cord (in the new born). For this reason three principal groups are recognized: *Tetanus traumaticus*, *tetanus puerperalis*, and *tetanus neonatorum*. The clinical symptom-complex coincides so thoroughly in these three groups that it may be described for all three simultaneously. Some few individual points will be mentioned at the end of this chapter. We shall also describe those few forms of tetanus which deviate from the three mentioned groups.

Prominent among all the symptoms of tetanus, in keeping with the localization of the principal amount of the toxin in the spinal cord are those relat-

ing to the *motor sphere*. There is scarcely a large muscle group in the body which is spared in the course of tetanus. Primarily and most severely, the muscles of the head and neck are attacked. A few days after the injury the patient notices (and the injury may be entirely unknown or unobserved by him, or this may occur after childbirth) a certain stiffness in the muscles of the neck and in the muscles of mastication. To this no importance is attached by the patient or by the physician who is called in; a beginning rheumatism an affection of the oral cavity, etc., is considered. The tragedy, which in a very brief time will take place is not suspected, but even after a few days, occasionally after a few hours—we shall describe the period of incubation at the end of this chapter—we are in the midst of the first act of this sad drama, which frequently enough in a very short time terminates tragically. The rigidity of the muscles of mastication, the masseter spasm, has become so great that the patient does not succeed actively, nor the physician passively, in separating the jaws from each other even to the distance of a millimetre; the musculature of the back of the neck shows board-like tension, the head is directed backward so that it bores itself into the pillow: *the stage of opisthotonos*. The facial expression of the patient is entirely altered, there is mask-like rigidity, the forehead wrinkled above, the eyes motionless, directed straight forward, the alæ of the nose widely dilated, the mouth increased in breadth and drawn downward, a symptom-complex which has been designated *facies tetanica*. To this, often in consequence of a spasm of the facial nerve a peculiar painful, grinning expression is added which for a long time has been known as the *risus sardonicus*, "*risus tantalicus*," we should almost call it; for the patient retaining his full consciousness disturbed in the most terrible manner by his affection, in spite of sensations of hunger and thirst, which the anxious nurse would only too gladly alleviate, is not capable of taking the smallest quantity of food, scarcely a drop of fluid, and in spite of all his torture is compelled to retain a constant smile upon his face, a symptom which at the onset of the disease often deceives the inexperienced members of the family regarding the severity of the affection.

Soon the musculature of the back and abdomen is attacked with rigidity. The vertebral column of the patient is bent forward and becomes so stiff that there is fear of breaking it if the attempt be made to move the patient. The tension of the abdominal muscles is board-like; the abdomen is completely retracted. If the extension of the body is completely straight, this is designated as "*orthotonos*"; occasionally the trunk is more bent forward or toward the side, positions which are known as "*emprosthotonos*," or "*pleurothotonos*."

Regarding the extremities, the upper often remain free, showing no symptoms; only in the muscles of the shoulder a certain immobility is sometimes noted. On the other hand, if the disease continues for several days the legs are almost always attacked with rigidity. This is especially marked in the muscles of the knee joint; the extension contracture may become so great that hyperextension appears. The feet and toes, on the contrary, are usually spared by the tetanic rigidity.

The musculature of the internal organs, in the further course of the morbid process also is attacked, and this stage frequently brings about the fatal termination. The diaphragm is most markedly affected; many authors

have called attention to this spasm, the painful sensation in the cardiac region of which most patients complain. By other clinicians the cause of this symptom is directly referred to spasm of the musculature of the heart.

When the muscles of respiration are implicated in this spasm the condition is most serious. This may cause sudden death, occasionally even without the other symptoms of tetanus being developed to a marked extent.

Although the patient suffering from tetanus is dreadfully tortured by the rigidity of his muscles, which has already been described, the measure of his sufferings is by no means full; the tonic spasms are even increased by a number of scarcely avoidable conditions. The slightest movement to which the patient is subjected, the faintest commotion in his vicinity, are sufficient to cause a paroxysmal excessive contraction of numerous muscle groups, which previously were already in a state of tension. An attempt to allay the agonizing thirst by swallowing a little fluid, the mouth having to be opened for this purpose, is responded to by the patient with a severe paroxysm of the muscles of deglutition; the attempts of the nurse to rearrange the bed cause an increase of the extensor spasm of the entire musculature of the trunk; the appearance of persons in the room of the patient, no matter how carefully and guardedly they have entered, the opening or closing of the door of the room, the opening of a window is sufficient to increase the spasm. For the most part these spasms are of a tonic nature; clonic spasms are comparatively rare. The increase of the spasms due to external circumstances is often accompanied by a piercing cry, which issues with difficulty through the tightly closed lips, without giving the patient any relief. Frequently there is added to this a peculiar grinding noise of the teeth, which is due to the marked trismus. As a rule, the patient is only able to give vent to unarticulated sounds, so that he is hardly able to make himself understood to those about him. If it is possible for him to speak a few words the speech appears "squeezed." This characteristic is often retained even during the stage of convalescence; only becoming normal after the trismus has completely disappeared.

In regard to other symptoms due to the spinal cord, *sensory disturbances* are comparatively rare. It must, however, be admitted that in the presence of such a severe affection which prohibits any unnecessary manipulation on the part of the patient, systematic investigations of sensory conditions have scarcely been attempted. Subjectively there is frequently an abnormal increase of the pain sense; especially in those muscle groups in which the spasm is marked, hyperalgesia is decided. In regard to the *reflexes*, the same may be said as of the sensory phenomena; they are rarely tested in tetanus; individual authors have occasionally noted a marked increase in the patella tendon reflex.

The *cerebrum*, as has already been mentioned, in the majority of cases, shows no symptoms. Shortly before death, delirium occasionally occurs; but in general, the mind, during the entire course of the disease, is clear, not to the advantage of the patient as we have already emphasized before. Only in alcoholics, who are attacked by tetanus, soon after the development of the symptoms, does delirium occur, and this is so constant that if a person attacked by tetanus shows delirium during the attacks it is almost certain that the affected individual is an alcoholic.

At this point the *insomnia* may be mentioned which frequently in the individual affected by tetanus cannot be combated by any known remedy. Whereas, as emphasized by Rose for example, the first symptoms of tetanus, trismus, the spasm in the musculature of the neck, develop after patients have passed the night in deep sleep, with the appearance of tetanus sleep is rare, and if it occurs at all, lasts but a few hours.

Compared with the symptoms due to the spinal cord, all others are secondary in importance. The *internal organs* during the course of the disease show but few pathologic changes except when complications occur which are not a part of the affection. Cardiac activity is frequently somewhat increased, the pulse rate amounting to 150 per minute. (The sensation of oppression in the cardiac region has already been mentioned.) The respiration is often increased. If the respiratory muscles are especially affected by the spasms and the thorax remains almost permanently in the inspiratory position, the patient is tortured by a terrible dyspnea, without being able to afford himself relief by bringing into play the auxiliary respiratory muscles. The dyspnea may finally become so great that deep cyanosis appears, the patient dying with symptoms of suffocation. A complication which is especially feared is pneumonia; this may occur as aspiration pneumonia, the result of regurgitated particles of food; secondly, on account of the insufficient mechanism of respiration, the result of spasm of the respiratory muscles, a stasis of the bronchial secretion readily occurs in the alveoli giving rise to hypostatic pneumonia. Although in general, pneumonia is not such a frequent complication of tetanus, this is principally due to the fact that death occurs before there is an opportunity for an inflammation of the lung to develop.

For the same reason a serious complication on the part of the *kidneys* and actual nephritis is but rarely observed. On the other hand the *urine* frequently shows pathological changes. Not rarely does it contain albumin and albumoses, further urobilin; in some few cases sugar is also found; an increased excretion of urates, creatin and creatinin have not been found as yet. That the absolute quantity of urine is constantly decreased and concentrated is not to be wondered at, on account of the small intake of fluids.

All the more marked, on the other hand, in most cases, is the *secretion of sweat*. Scarcely has the nurse dried the forehead of the patient, when large pearls of sweat are again noticed. At other parts of the body the skin is mostly very moist, the bed sheets after a few hours are wet from sweat, an unfortunate condition for careful nursing, which however, cannot be avoided even with the greatest care. In consequence of the excessive secretion of sweat and on account of the difficulties regarding the care of the patient, various cutaneous affections very frequently occur, eczema and bed-sores; nursing is powerless, as a rule, in the avoidance of these complications in tetanus.

In some cases, simultaneously with the secretion of sweat, the *secretion of tears* is increased, then the face of the patient presents a very remarkable appearance. Over the smiling countenance (*risus sardonicus*) tears are constantly flowing; and as paradoxical as it sounds, one might almost say: "The patient cries because his disease forces him to laugh."

Finally, we must mention an especially interesting symptom of tetanus:

The condition of the temperature. In many cases, up till a few hours before death, the temperature does not exceed 102.2° F.; in other cases, a short time after the appearance of the tetanic symptoms there is a rise of temperature up to 105° F. and even higher, a fact that was even known to the physicians of the eighteenth century, de Haen, Dazille and others. The cases running their course with these very high temperatures, in general, usually offer a very unfavorable prognosis; recently v. Leyden mentioned, in a clinical lecture, which shall be reported further in the chapter on therapy, that he had no knowledge of a case of tetanus in which after the temperature had risen to 104° F. recovery had ever occurred. Especially remarkable is the rise of temperature shortly before, and frequently a few hours after death. During this period temperatures of such height are reached as are not found in any other disease: *Post mortem temperatures of 109.5° F. and 111.2° F. are not rare*; they occur immaterial whether the patient, prior to death, has shown but slight or marked rises in temperature. This fact has also been known for a long time, even Wunderlich having called attention to it. A satisfactory explanation for the appearance of these hyperpyretic temperatures has as yet not been given; some authors believe that they are nothing more than a phenomenon occurring in the cadaver similar to post mortem discoloration; others refer them to paralysis of the heat-regulating centres in the spinal cord. The cause of the post mortem rise in temperature cannot be looked for in the increased muscular action due to the spasms, for many cases which during the entire course of the affection are attacked by the most intense spasms never show temperatures of over 102.2° F. Nevertheless, in keeping with the modern standpoint, which the question of tetanus has now reached, we should like to propose the hypothesis, in explaining the appearance of these abnormally high temperatures, that *in many cases shortly before death a toxin combination of the tetanoid substance with the tetanus toxin occurs in the cells of the heat centre*. This hypothesis finds its support, partly in the results of subdural injection: If various chemical substances, for example, solutions of iodine, are injected into the subarachnoid space, a decided rise in temperature occurs in a brief time. In these cases, we must also assume that the substance in question at least produces an irritation of the cells in the heat centre or has formed a chemical combination with them. This explanation of the appearance of pre-agonal or post mortem rises of temperature cannot be regarded as an explanation for all diseases; besides chemical irritation which acts upon the heat centre, there are also purely mechanical ones which show similar effects upon the heat centre. This latter hypothesis explains the high rises of temperatures which are occasionally observed after severe injuries of the cervical cord and of the medulla oblongata.

Whatever explanation is accepted, regarding post mortem rises of temperature, its occurrence is certainly remarkable and often has a very strange effect upon laymen. A few drastic examples are given by Rose in his excellent book; he describes several cases in which in the presence of nurses, he confirmed the fatal termination in patients dying from tetanus and then left the hospital; a short time later the nurse came running into his room with the report: "Doctor, you must have made a mistake, for the patient is not dead, he is only beginning to develop a terrible fever!" The post mortem rise

in temperature does not last for a long time, three quarters of an hour after death the cadaver begins to cool (according to Rose's records).

PROGNOSIS, COURSE, DIFFERENTIAL DIAGNOSIS OF TETANUS

After having mentioned the principal symptoms of tetanus, a few words regarding its *course* and *prognosis*, also in reference to the *varieties* of tetanus which deviate from the usual form and the *differential diagnosis* will be in place.

Numerous prolonged investigations, in the human subject, are necessary before definite opinions could be given in regard to the number of days that elapse, after an injury, before the symptoms of tetanus appear. Many patients cannot remember having injured themselves at all; on the other hand, prior to the era of the discovery of the tetanus bacillus no importance was laid upon the etiological relation of trauma; in all cases in which injury could not be determined, nontraumatic or rheumatic tetanus, etc., were spoken of. But even after Nicolaier's bacillus had been recognized as the causative agent of all forms of tetanus and after numerous animal experiments had been made with it, or with its products, the question, regarding the **stage of latency** of human tetanus, could not be solved. In the first place it was shown that various kinds of animals differed greatly regarding the *period of incubation* of tetanus; secondly it is in the nature of the experiment that we cannot compare these results with the natural forms of infection which occur in man: In the experiment we utilize the finished products of tetanus bacilli, the toxins, at one, usually a lethal dose, by subcutaneous or intravenous injection into the organism of the animal that was previously entirely well; in man, at first but few bacilli enter the wound, they increase and only after several days, or at least after many hours, produce the poisonous substance which enters the circulation and the organs in small amounts from the wound. As valuable, therefore, as animal experiments are, which have been carried out to explain all questions regarding tetanus, a certain reserve must be adopted, in the comparisons of results with those produced naturally from the morbid changes occurring in the human organism. This is particularly necessary in regard to the period of latency of tetanus; here only the results carefully investigated in the human being are of value. Rose, who perhaps has the best knowledge of tetanus, having observed numerous cases of his own, upon the basis of these as well as according to the results of other authors, believes that in one-half the cases of tetanus, only in the second week after the injury and in a third of the cases only in the third week, in all other cases from the third to the sixth week, do the symptoms arise. Some authors have even suggested a period of latency up to sixty days. An immediate, an abrupt appearance of tetanic symptoms following the injury is absolutely denied by Rose.

PROGNOSIS

In direct connection with the period of incubation of tetanus is that of prognosis; to-day it is a well-founded law that the more rapidly the symptoms develop after trauma the more unfavorable the chances of recovery.

Rose calculates from his observation that 91 per cent. of all cases terminate fatally after an early development of symptoms, 81.3 per cent. from late, 52.9 per cent. from latent cases and only 50 per cent. from cases in which the symptoms appeared very late. These figures coincide, in general, with the reports of most other authors. The results of statistics since the discovery of the antitoxin are different and this will be shown in the last section of this article where we shall have to refer again to the prognosis of tetanus; for the mortality of tetanus, which had been estimated prior to the introduction of specific treatment and showed that from 80 per cent. to 90 per cent. of all cases in the last few years had proved fatal, has become decidedly lower. Besides the rapid appearance of the first symptoms of tetanus, other conditions also show an unfavorable prognosis: First, fever of over 103° F. at the height of the disease, further, complete trismus which makes it impossible to take nourishment of any kind, then the frequency and the intensity of the tetanic attacks, complications on the part of the musculature of the respiratory and deglutition apparatus. Any one of these symptoms is sufficient to cause death in a very brief period; if several of them are combined the prognosis is absolutely hopeless. As a rule, the fatal termination occurs a few days after the appearance of the first symptoms; tetanus may be considered as one of the most deadly diseases of which we have any knowledge. At the same time the term "treacherous" may also be applied to it: Often enough after the patient is already in the second week of the disease, after the severest symptoms have lessened in intensity and the physician is hopeful of the early recovery of his patient, suddenly spasm of the respiratory musculature occurs and death takes place. It is, therefore, advisable for the physician in every respect, in treating a patient with tetanus, to be very guarded in his prognosis even in an apparent mild and favorable case, and to point out to the family of the patient the grave danger up to the point of an almost complete recovery.

That this recovery requires a long time, even in the mild cases, need not be explained after a description of the extraordinarily severe general symptoms of tetanus. A few words regarding the *individual varieties of tetanus*.

VARIETIES

The course of **traumatic tetanus** and **puerperal tetanus** is almost identical; both forms owe their origin to an external wound in which the bacilli enter; that puerperal tetanus arises in any other manner than from Nicolaier's bacillus must be rejected as erroneous upon the basis of recent investigations and observations. The most frequent causes for the development of puerperal tetanus are the attempts of pregnant women themselves, or of quacks, to bring about abortion. Further, unclean manipulations during labor are also important factors. Occasionally, however, even in well conducted obstetrical clinics, cases of tetanus puerperalis occur; then the degree of circumspection and the strict control of all factors are necessary to prevent an endemic in the hospital in question. If tetanus occurs in a pregnant woman who has not aborted, the pregnancy is not always interrupted by tetanus, thus Rose reports a case of enteric fever and tetanus which terminated fatally; at the autopsy

there was found in the interior of the uterus in an intact amnionic sac, a fetus which measured 5 cm. Brambilla has even reported the clinical history of a patient seven months pregnant who after pricking her foot was attacked by tetanus, suffering for twenty days from the attack, and after thirty days giving birth to a completely healthy girl and finally herself recovering.

Such cases, however, belong to the greatest rarities. In general if death does not occur previously, tetanus causes abortion. Attempts to bring on labor, in view of the severe affection in which even the slightest manipulation causes an increase of the spasm, are not to be considered. Only in those cases in which marked dyspneic phenomena, as a result of spasm of the muscles of respiration are present, must the physician put the question to himself whether by an artificial interruption of the labor he may ameliorate the condition of his patient.

Tetanus neonatorum does not differ markedly from the two previously described forms. Its occurrence can only be explained in the manner that the bacillus of tetanus enters the umbilical wound. All previous opinions regarding tetanus neonatorum, which in its clinical course was known to the physicians of ancient times, must be rejected upon the basis of scientific results of investigations of the last decade. As we have seen, tetanus is a form of "dirt disease," i. e., depending upon bad hygienic conditions and insufficient aseptic procedures. It is not remarkable that tetanus neonatorum occurs particularly among the poorer classes. It does not occur very frequently in Europe, epidemics of tetanus belonging to the greatest rarity. On the other hand, according to the reports of individual physicians, who have practised for some time in the tropics, the affection is said to decimate the population in some countries; thus, for example in Cayenne, Jamaica, Guiana, 10 per cent. to 25 per cent. of all negro children perish from tetanus neonatorum. It is very conspicuous that children born of whites and Indians in the same region and under the same hygienic conditions, are much more rarely attacked by tetanus. Baginsky, from whom we have taken these latter facts, quite properly refers to this varying condition of the individual racial peculiarities in regard to the same disease, for in tetanus this may be explained as a "racial predisposition."

Tetanus neonatorum occurs most frequently at the end of the first and at the beginning of the second week of life of the infant. This may be explained in that under normal conditions, upon the fourth or fifth day the cord falls off and the affected area until then covered by skin, therefore, up to the end of the second week, represents an open wound. If this area is not kept hygienically and aseptically clean, the danger of entrance of the tetanus bacillus is present. If now we are asked, why, in spite of the dirt which exists for the great part still in the dwellings of our poorer population, tetanus neonatorum is a comparatively rare disease, three reasons may be given: 1. The already mentioned racial predisposition; 2. The circumstance that the tetanus bacillus occurs particularly in earthy floors, more rarely in the dirt of rooms and in dwellings in larger cities; 3. The constitution of the umbilical wound itself. As this represents a fresh granulating surface and frequently suppurates more or less, numerous young active leukocytes are present; these are capable, as we have mentioned at another place, to resist the tetanus bacilli

which attempt to enter, in case the bacilli are not present in too large amounts and their toxicity is not too great.

In general, regarding the course of tetanus neonatorum, the characteristic first symptom must be particularly emphasized, which has been known to physicians for a long time: Parents and physicians are often notified of the onset of tetanus in the new born by the fact that at the moment at which it attempts to nurse, the child lets go with a painful cry—the first symptom of the beginning spasm of the masseter. I should still like to mention that—although we have not observed a case of this kind—according to Soltmann the first symptom of tetanus neonatorum is a characteristic contraction of the face. In general the course of the tetanic spasms and the other clinical symptoms will not differ from that of traumatic tetanus.

As the fourth form of tetanus which is still described by some authors, **rheumatic tetanus** must be mentioned. There are said to be cases which show the characteristic picture of tetanus without the bacillus of Nicolaier being found in them. We do not recognize this form; if we reflect that occasionally the smallest wound, the origin of which may not even be noticed by the patient suffices to permit the entrance of the tetanus bacillus, and that in such cases after six or eight days the first symptoms occur, even with the most careful investigation the determination of this injury is impossible, we must admit that it is entirely erroneous to give to such cases a particular standing and attempt to refer them to refrigeration and other causes. We believe, therefore, that the more accurate bacteriologic diagnosis becomes, particularly in those cases in which the etiology is known, and also animal experiments, i. e., the inoculation of several animals with the blood obtained from patients by venesection, the more rarely will it be necessary to make a “dilemma diagnosis” “rheumatic tetanus.” In this connection it is well worth mentioning that lately also tetanus bacilli have been found in the sputum.

In contrast to the last described form of tetanus, we must, however, recognize another: **tetanus facialis**. It is particularly the merit of Rose to have described this form of the disease, its characteristic course and to have suggested a theory for its manner of appearance. In the description of tetanus facialis we shall adhere closely to that given by Rose. Tetanus facialis differs from all the previously described forms of tetanus in that in this instance we are not dealing with spasms of distinct muscle groups only but simultaneously even previously with a true paralysis in the course of a nerve, and particularly in the facial nerve. Facial tetanus occurs after an injury has happened to the head in the course of the facial nerve; paralysis of the face constantly occurs on the side of the trauma and frequently at the onset of the disease; it affects all regions supplied by the facial nerve except the internal ear and the parts covered by the chin. The paralysis is not in direct connection with the other symptoms of tetanus, this may be seen from the fact that cases of general traumatic tetanus occur in connection with wounds of the head without facial paralysis occurring as a complication. Among the peculiarities of *head tetanus*, Rose emphasizes the frequency of spasms of deglutition which occur in its course; the proportional long duration, as well as the milder course of the affection. He refers the seat of the paralysis to the distal end of the Fallopian canal at the stylo-mastoid foramen. But how

to explain that particularly after injuries to the head the area of one nerve should show paralytic conditions, this is still a debated question; we shall not enter upon the discussion of these diametrically opposed views but shall leave this question as a problem to be solved by the future.

DIFFERENTIAL DIAGNOSIS

After having described the individual varieties of tetanus we must briefly refer to the *differential diagnosis*. If tetanus is well developed the diagnosis is easy. With the appearance of the first symptoms, however, especially if reports of preceding injuries are absent, errors may readily occur. A number of affections of the jaw and the oral cavity may produce *trismus-like conditions*. In general, however, by an accurate examination and palpation of the affected portions of the body, it can be readily determined whether local conditions cause the disease, or upon their removal the question of a beginning tetanus is to be considered or not. Among general diseases the symptoms of which may give cause for confusion with beginning tetanus there must be mentioned, *meningitis*, *hydrophobia* and *poisoning with strychnin*. Differentio-diagnostically, besides the important data obtained from the history, that in meningitis and in hydrophobia the significant and early symptom of tetanus, trismus, is almost entirely absent, that in meningitis usually severe cerebral phenomena are present which in the case of tetanus, as already mentioned, belong to the greatest rarity, that in poisoning by strychnin in contrast to tetanus usually the extremities mostly markedly develop the severe spasmodic phenomena will be decisive.

THERAPY

In the discussion of the therapy as may have been gathered from what has been previously said, we find ourselves presented with one of the most difficult problems of internal medicine: In the first place tetanus, up to this time at least, has been one of the most fatal of all infectious diseases; secondly its symptoms are such that the comforts of general nursing, which have made such great advances in the last few years, can only help the patient to an exceedingly limited degree.

There are four distinct indications which our therapy must reach in the treatment of tetanus: 1. The treatment of the wound, the point of entrance of the bacilli; 2. General nursing and diet; 3. General medical therapy; 4. Specific curative serum therapy.

We shall begin with the description of the *treatment of the wound*. Even before the discovery of the cause of tetanus, attention was directed by physicians to this point; this was based upon the fact attained by experience, that tetanus often occurs in connection with injuries from wounds and that in connection with trauma, if treated at once by radical measures, at least in many cases recovery occurs. The treatment, therefore, was not limited to a thorough cleansing of infected wounds, but incision and excision were practised, sometimes complete amputation of entire members of the body with the hope that the toxic product would be completely removed from the organism. This manner of surgical treatment, however, after the bacillus of tetanus was

discovered and the manner of its activity had been learned, has been variously modified. As the toxin produced by the bacillus of tetanus does not act in the wound itself but is carried extraordinarily rapidly by the lymph channels and circulation to the central nervous system, it is advisable to extend surgical treatment to wider areas than to the wound itself. Here, naturally, energetic measures are necessary; for, on the one hand, as we have seen, the bacilli of tetanus are extraordinarily resistant to external influences, chemicals, etc., and, on the other hand, may remain in the wound in an animate condition for days, constantly producing fresh quantities of toxin, and in this manner cause a constant increase of toxicity in the organism. The treatment of the wound must therefore be directed in two different ways: 1, prophylactically; 2, directly (upon outbreak of the first symptoms). Regarding the prophylactic treatment, there is not much to be said in our present aseptic era; there is probably no surgeon to-day who does not thoroughly cleanse every wound before he carries out any other method of treatment. But especially in regard to the danger of infection with tetanus bacilli, attention must be directed to such injuries as are contaminated by earth. Here the most thorough disinfection with the strongest chemicals or with a hot iron is necessary, to destroy the bacilli which have entered the wound with the particles of earth, before they have begun to display their deleterious action.

If, however, the first symptoms of tetanus have appeared in a patient, it is the duty of the physician in all cases—also in those in which the patient denies an injury—to examine the body most carefully, so as to determine if possible the point of entrance of the bacilli. If this succeeds, the game is by no means won as yet; for at the period of the outbreak of the first symptoms a certain opinion can never be given how much tetanus toxin has already entered the substance of the central nervous system. But nevertheless in an early and energetic treatment of a wound infected by tetanus bacilli, the chances for the recovery of the patient are decidedly more favorable than if these measures had not been carried out because the point of entrance could not be found. By an energetic treatment of the wound, we understand the use of strong corrosives and disinfectants, secondly, the hot iron, and thirdly, deep incision of the wound, or even excision of the surrounding area (extirpation of the wound). We advise against the amputation of an extremity for the purpose of radical removal of the point of entrance of an infection for reasons given above.

Although quite definite advice may be given in the treatment of wounds, this is unfortunately not the case regarding nursing of the patient. This can only be carried out in the minority of cases, in keeping with what is considered good nursing to-day. Nursing must be limited particularly to the surroundings of the patient, the sick room, etc., for, as we have seen, even the slightest noise or movement in the surroundings of the patient is sufficient to cause an increase of his spasm. Care must be taken that the sick room is isolated as much as possible, therefore, not near the street, where passing wagons often shake the entire house, or toward the yard where carpets are beaten daily, children in playing make noise, etc. To prevent the entrance of sound through the doors they are to be covered with thick portières; upon

the floor of the sick-room—in contrast to the furnishing of other sick-rooms—thick carpets are to be laid. Nurses should go about with felt shoes; as few as possible should enter the room, these should be experienced in all branches of nursing. All unnecessary waiting around in the sick-room is to be prevented; all visits even of relatives is to be prohibited until the spasms in the patient have permanently disappeared. The light in the bedroom is to be shaded; perhaps the new discoveries of chromotherapy, by the introduction of distinct light effects in the bedroom, may be able to bring about a quieting effect upon the patient! The sudden entrance of waves of sunlight into the bedroom must be avoided as this may give rise to the development of new spasmodic attacks.

Care is necessary in the selection of a *bed*. This should be as broad as possible, so that the danger of the patient falling out at the side during a convulsion is diminished. It should stand so that it can be approached from both sides. The patient is to be placed upon a feather bed or a large water bed; the severity of the spasms is decidedly diminished by this. The covering should be light; all bedding or clothes which press upon him only add to the increase of the spasm in general, and lead particularly to dyspnea. The night shirt for this reason should be as wide as possible, the collar remaining open. Regarding the pillows, it is advisable to limit their number to one or two so that the patient cannot bore himself too deeply into them, compelling him to assume a position as nearly horizontal as possible. It is self-evident that there must be a space between the patient and the upper end of the bed to prevent the head striking during an extensor spasm.

But even when all these precautionary measures have been followed accidents may occur owing to the nature of the affection; for this reason the nurse must not leave the bedroom for a moment, constantly keeping the patient in sight. Therefore, at least two nurses are necessary in every case of tetanus, who should relieve each other every twelve hours; in severe cases it is even advisable to have two nurses on duty together. Besides the nurse, another person should be present outside of the sick-room, so that orders can be taken, such as the bringing up of food, bed-pan, etc. Loud or prolonged talking is to be absolutely prohibited. Questioning the patient should be limited to a minimum, and so arranged that the patient can answer with a brief yes or no.

Only the most necessary manipulations are to be carried out for the patient. Too frequent change of bed- and body-linen should be prohibited; this is a difficult matter to carry out for a careful nurse, for the bed- and body-linen of the patient often as a result of the profuse sweating is wet through and through. The care of the skin of the patient is also to be limited; naturally, parts of the body that have been injured by the patient during his attacks, cutaneous emphysema, bedsores which often arise as a result of sweating, must be treated in a proper manner. By careful sponging the marked perspiration may be removed, the nurse must be instructed to be cautious in approaching the bed so as not to knock against it, as this is likely to produce a fresh attack. The temperature, unless there be very special reasons should only be taken twice a day, and the fact should always be kept in mind that during the time that the thermometer is in the axillary cavity the

patient may have an attack and thus break the thermometer [for this reason the temperature should never be taken in the mouth]. The urine is to be voided into a suitable apparatus, the bed-pan should not be placed under the patient. Before the bed-pan or the urinal is used by the patient it should be warmed or covered with flannel as the contact with cold metal or porcelain is liable to produce a fresh spasmodic attack.

The *nutrition* of the patient is one of the most difficult cares of the nurse in tetanus; this is partly the reason why, in spite of the greatest care on the part of the nurse, we frequently do not succeed in maintaining the powers of the patient. Many patients do not succumb to their actual disease, tetanus, but to gradual exhaustion; they do not have sufficient power to withstand their disease. If the trismus is absolute, no force, no matter how great, is capable of opening the jaws, even to the extent of a few millimetres; on the contrary, endeavors of this kind only increase the masseter spasm. Then there is but one remedy, besides artificial nutrition, which is to be considered, to narcotize the patient. During the narcosis, when the spasms have ceased entirely, introduce the stomach-tube and thus pour nourishment into the stomach. This manner of nutrition, however, is never sufficient and cannot be carried out exclusively; for in the first place the amount of fluid introduced into the stomach by the stomach-tube is limited; further, it is a serious matter to anesthetize a patient every day, not to say several times daily; and finally, the nutrition, by means of the stomach-tube in unconscious persons, therefore, in those under the influence of a narcotic, constantly carries with it the danger of an aspiration pneumonia, which may occur in removing the stomach-tube. In severe cases, in whom, as the result of trismus, nourishment by the mouth is impossible, and further in those in whom no absolute trismus is present but who can only take very small amounts of fluid on account of the small opening between the teeth, we are compelled to resort to *artificial alimentation*.

Two methods may be adopted: by the rectum and subcutaneously.

That the first method, in severe cases in which the slightest movement produces a spasm, is a two-edged sword does not require further explanation. Even if three persons acting simultaneously and with the greatest precision give the patient a nutritive enemata, two who lift him and the third one introducing the rectal tube, this means great exertion on the part of the patient. It can scarcely be avoided that some fluid will be spilled and fall upon the bed clothes; frequent change of bed clothes, as has already been mentioned, is to be avoided. Then the fecal evacuations must be considered which naturally are more frequent in nutrition by rectum than in other modes of nutrition—also an undesirable factor in the treatment of tetanus; briefly, all these reasons are against nutrition by rectum, which in numerous other diseases quite properly plays a predominant rôle; in tetanus at least during the acme of the disease in which the spasms are so prominent, it is not advisable.

For this reason we advise another method of artificial nourishment: *the subcutaneous method*. In regard to the method, the manner of preparing the fluids to be injected and the amounts and the intervening periods, the manner in which they are absorbed from the skin so as to be utilized by the

organism as nutritive products, a too minute consideration of all these points would take us too far from our subject matter. Accurate descriptions will be found in the large collective work of Leyden, "Handbook of Dietetic Therapeutics," in the article written by Leube. I should only like to emphasize that naturally all preparations for subcutaneous infusion in tetanus should be carried on outside of the sick-room. The disinfection of the small cutaneous area, on the lateral aspect of the thigh, into which the needle is to be introduced, is to be carried out as rapidly as possible; then the needle is to be introduced with a single strong effort, at once, under the skin, and the fluid should be allowed to flow gradually under the skin and thus to distribute itself. After the entire quantity has entered, the needle is rapidly withdrawn and the point of entrance immediately closed with iodoform collodion. From this brief description, it will be seen that this method of subcutaneous nutrition is much easier for the patient than that form introduced by rectum; and if I am asked whether the patient receives as much advantage from this method as from the other, a simple calculation will give the answer: The best and richest nutritive enema which can be chosen at all is a meat-pancreatic enema, containing about 650 calories, and this is given to the patient with the presumption that he retains the entire enema and absorbs it completely. An infusion of 200 cc. of olive oil, a quantity which may be readily introduced under the skin of the patient at one time, has a value of 2,000 calories, and certainly of this nothing is lost to the patient, for scarcely a drop will flow from the small point of injection which has been carefully closed after the operation. Finally, I should like to emphasize that all injections, at least within the course of the week, may be made into the same thigh.

Fortunately, however, we are not always dealing with such severe cases. If the trismus is not absolute and the patient is able to open his mouth at least a few millimetres, and finally if no spasm of deglutition is present, the attempt should be made to give him small quantities of fluid frequently during the day. These substances must never be given out of vessels that are breakable; for if at the moment at which a porcelain dish, for example, is placed between the teeth of the patient an attack of trismus should occur, the teeth which are forced tightly against each other will undoubtedly crush the porcelain and thus numerous fragments will find their way into the mouth of the patient. Therefore, either metal spoons, metal cups, etc., are to be used, or nipples of rubber may be utilized with advantage. By the latter method the patient may be able to take the fluid in any quantity he wishes; this obviates the pouring of fluid into the mouth which is very objectionable to many patients. A wedge or mouth-gag introduced between the row of teeth and an attempt made to forcibly open the jaws is absolutely unnecessary in my opinion. By all these manipulations the spasms, especially that of the masseter muscles, is almost always increased. However, it is advisable in patients in whom teeth are missing to utilize these spaces in introducing nourishment.

Fluid dare never be given to the patient without directing his attention to the fact so as to prevent regurgitation. How readily the complication of aspiration pneumonia occurs has already been described.

Definite rules regarding the food which is to be given to the patient

cannot be indicated; the taste of the patient may decide; he should never be forced to take food which in health is repugnant to him.

The fundamental principle, according to which nutritive substances must be arranged is this: In as small a quantity of fluid as possible materials rich in calories, having an agreeable taste, non-irritating and easily digestible, are to be administered. Milk rich in fat or very strong bouillon, beef-tea containing eggs, accordingly the addition of materials containing nutritive substances would also be advisable in the severest days of the affection. Cocoa and chocolate may be given by way of variety; patients who in health show no aversion to cod-liver oil may also take this three or four times daily on account of its high nutritive value. The patient may have cold tea, cold coffee and lemonade several times a day; on account of the danger of regurgitation pellets of ice should not be given. Alcohol had better not be given, although its nutritive value is by no means slight; but it very readily causes excitation which has a bad effect upon the patient. Carbonated drinks, particularly champagne, are to be prohibited, for apart from the excitement to which they may give rise, their contents of carbonic acid readily cause deglutition spasms. On the other hand, heavy beer, such as Culmbacher, porter, in case the patient is used to taking them, may be given to the patient. All solid and even semi-solid food such as vegetables, rice, egg-foods, poultry, boned fish, etc., cannot be given at the height of the disease; as soon as this period is passed, a plentiful use may be made of these substances. Stimulating treatment in the period of convalescence does not differ from that resulting in other severe exhausting diseases.

We must still say a few words regarding *baths and hydropathic treatment*. There are authors who advise the former very strongly for tetanus; and it must not be concealed that well regulated baths have a decidedly favorable sedative influence upon the spasms. Against their use, however, is a factor which in my opinion is of pre-eminent importance: this is the question of transporting the patient to the bath-tub. And in view of this question, it must be frequently considered whether the advantages which the patient obtains from the bath are more important than the results due to the manipulation necessary in placing the patient in the bath. This question will have to be decided with a positive No! I believe that baths should only be given in tetanus if the general circumstances are most favorable. In private houses especial arrangements must be had so that the patient may be lifted immediately from the bed into a sufficiently large bath-tub, carried by at least two careful nurses: transporting the patient a greater distance to the bath-room, under some circumstances, through narrow doors, etc., is combined with too great inconvenience for the patient. Such disadvantages would decidedly contraindicate the use of the bath. In hospitals the use of baths in tetanus patients is greatly facilitated by modern improvements, the patient being lifted directly from the bed into the bath. If an arrangement of this kind is not at hand the same principles should be laid down for the use of the bath in private houses as is operative in hospitals. In my opinion, the temperature of the water should be warm; even patients with high temperatures should not be placed in cold baths; the shock which follows, which acts so favorably in other diseases with high temperature, especially in enteric

fever and in pneumonia, in the case of tetanus, on the contrary, causes an increase of the spasm. Only with one modification, therefore, can cold baths be given, in case they are looked upon as at all necessary for the patients. The patient should be first placed in a warm bath (about 95° F.); gradually cold water is allowed to flow in, until finally, in the course of fifteen to twenty minutes, a temperature of from 78° F. to 80° F. is reached. In general, however in tetanus, in patients that have but slight fever, warm baths of from 95° F. to 100.5° F. are useful on account of their sedative action.

Tubs supplied with rubber wheels which may be rolled to the bed-side of the patient, must be so constructed that the patient may lie comfortably in them and not injure himself in case a spasmodic attack occurs while he is in the water. Regarding the duration of the baths in case the condition of the patient allows, they should be prolonged for some time, in order to gain their complete sedative influence. Thus, if the spasms cease, while the patient is in the bath-tub, food, etc., may be given. On the other hand, in tetanus it will rarely be possible to give the patient a bath several times a day as is done in enteric fever. The question, therefore, arises, whether it does not appear advisable to give *permanent water-baths* in tetanus (a method of treatment which was employed by Riess and others, a number of years ago in tetanus). Personally I should favor this in the treatment of cases in which favorable conditions of a treatment of this kind in a permanent water-bath are present; i. e., on the one hand, there must be a complete arrangement for this method of treatment; permanent water-baths cannot be improvised. Secondly, the nurse must keep the patient in the bath constantly in view; sudden death by drowning in the bath has been reported several times in literature; almost all of them the results of negligence on the part of the nurses. Thirdly, the patient must be comfortable in the bath; and, fourthly, finally, the objective observation decides whether the number and intensity of the spasms are less in the bath than when he is in bed. If all these requisites for the use of the permanent water-bath are favorable it offers two decided advantages as compared to the treatment in bed: first, the patient in the bath-tub notices the movement of other persons in his surroundings decidedly less than when in bed; secondly, the dangers from cutaneous eczema, bed-sores, etc., complications which so readily occur in tetanus, are almost entirely obviated if the patient is treated in the permanent water-bath.

If proper arrangements for bathing are not at hand, other *hydrotherapeutic procedures* may be thought of, but before their use is decided upon, the question must always be answered whether the use of the pack—for this is the principal method—may not produce an increase of the spasms. In patients in whom the spasms are well developed, the complete pack can hardly be utilized and cool packs should not be used; against the use of the latter, the same conditions are decisive which have been mentioned against the treatment by cold baths. But even a moist warm pack does not appear to us to be very valuable in many cases of tetanus; neither in those in whom the slightest manipulation is sufficient to increase the intensity of the spasm, nor in those in whom a profuse excretion of sweat, belongs to the most prominent clinical symptom. To increase this latter by packs, in my estimation, means to weaken the patient unnecessarily; and as the intake of fluid at the height

of the disease is a very limited one even without this, there is no indication to artificially increase the excessive secretion of sweat. If, however, the previously mentioned indications against the use of the moist, warm half packs may not be mentioned, a trial may be made to see whether they produce a sedative influence upon the patient.

These descriptions of hydrotherapeutic measures, the object of which, above all, is the quieting of the patient, lead us to the consideration of those remedies which are advised for a similar purpose. It would require too long a time to describe the history of all of these remedies, as well as the reasons why individual authors have advised their use in tetanus. Anyone especially interested should read the chapter "Die Sopientia" in Rose's work; there all the details will be found referring to this subject. I shall only mention those remedies, which, according to experience, act with certainty upon the spasms. In general, it may be mentioned in advance, that the doses of the narcotics which are employed in tetanus are frequently decidedly above the maximum dose of the drug, and that if an effect is to be produced by the individual remedy, it is well not to be too cautious with the size of the dose. This is primarily true of the remedies which are of the greatest importance in the treatment of tetanus: *opium* and its derivatives. Its advantages in tetanus are unquestioned; it diminishes the intensity of the spasms and acts upon the insomnia which, in general, is one of the most difficult symptoms to alleviate in tetanus. Among the preparations of opium which are to be particularly mentioned are the deodorized tincture of opium, 15 to 20 drops four to five times daily, further, the preparations of morphia which, as Rose quite properly maintains, are more valuable than opium on account of their composition being more constant. Among the preparations of morphia, the hydrochlorate appears to be the most suitable; from $\frac{1}{4}$ to $\frac{1}{3}$ of a grain may be given every two to three hours, daily. In severe cases, these doses may even be increased. If absolute trismus is present, these drugs may even be given in the form of suppositories or of enemata or by subcutaneous injection. Injections of morphia are most suitable for those cases in which it is advisable to produce a quieting result upon the patient so that special operations, etc., may be undertaken (treatment of the wound, subdural injections, etc.).

Next to opium, *chloral hydrate* deserves the greatest confidence in the treatment of tetanus. It has been utilized for over thirty years and we owe the introduction of this drug in the treatment of tetanus to the celebrated surgeon, v. Langenbeck. Since that time it has been frequently used by physicians in the treatment of tetanus, partly in extraordinarily large doses; and even if it does not produce a curative result in many cases, it constantly has a very calming influence. The dose which is usually employed is 2 grams (30 grains) three to five times daily; but even with this the drug in severe cases must be increased beyond its maximum dose. As an illustration of this, a case which was described by Berger, in 1892, and which Rose mentions in his book, may serve. A patient who fourteen days after a trauma developed the first symptoms of tetanus. Upon the fourth day after the appearance of the symptoms he received 12 grams of chloral hydrate, the same dose was given

up to the tenth day. Then for four days he received 18 grams each day, then upon one day 20 grams, and finally, upon the next day, 22 grams. With slight pauses during the next twenty days, daily 12 to 20 grams were given. The total quantity of chloral hydrate which the patient received inside of thirty-one days Rose calculates at about 500 grams, i. e., 16 grams daily upon the average!

The disagreeable irritating taste of chloral hydrate may produce deglutition spasms, but this may be somewhat disguised by the addition of a corrigent; we usually add to a solution of 15 grams in 150 grams, 10 grams of acetum rubi idæi and 25 grams of simple syrup. Chloral hydrate is very suitable for administration in the form of suppositories (2 to 5 grams); it is not suitable for subcutaneous injections on account of the danger of producing abscesses; it has frequently been given in combination with morphia; upon the basis of our own experience we may decidedly advise this combination.

Among other sedative remedies which, however, are less certain, and, therefore, not in such common use in tetanus, there may be mentioned the bromides, trianol, paraldehyde, amyl hydrate, urethan, injections of sulphate of atrophia and of hydrobromate of conium. Regarding their dosage, the same must be said as of chloral hydrate; to produce an effect, they must frequently be given in doses far exceeding their ordinary maximum dose.

A certain position, apart from the remedies previously mentioned, on account of the direct action upon the irritability of the motor nerve-ends in the muscle, must be given to two other remedies, these are *curarin sulphate* and the *preparations of calabar bean*. Against the use of the former, is the extraordinary variation of its composition. Almost all authors advise, before curarin is used in man, that an opinion should first be gained in an animal experiment regarding the degree of its toxicity. To make such experiments in the case of tetanus, in which delay is very precarious, may result in the fatal issue of the case and, for this reason, it is not advisable. This is all the more the case in regard to a remedy, the therapeutic value of which has been by no means settled as yet. If, however, the physician is in possession of a preparation of curarin of which he knows the absolute strength, it may be used in tetanus in the form of injection; for this purpose a solution of 0.1 curarin, 10.0 of water is made and $\frac{1}{4}$ to an entire syringe-ful is injected. Somewhat more constant in its composition than preparations of curare are the newer preparations of calabar bean, *physostigminum salicylicum*, and *physostigminum sulphuricum*. They may be given both internally and also in the form of injection; their maximum dose is 0.001 pro dosi; 0.003 per day. Remarkable results have not been attained with these preparations up till now.

Still to be mentioned, on account of the authority of the clinician who advises the preparation, is *salicylic acid*. Strümpell has noted favorable results in tetanus by the use of $7\frac{1}{2}$ grains given hourly. In the period in which tetanus was supposed to be a rheumatic affection, in many cases the use of this remedy appeared indicated; we cannot plainly see to-day how the preparations of salicylic acid are to influence the process of toxin production and of toxin chaining by the tetanoid substance of the central nervous system.

The same thoughts occur in reviewing another method of treatment which

belongs to the most modern and which has been advised by very celebrated investigators; it is the treatment by injections of carbolic acid. Baccelli, Paolini and others have developed this method. They inject daily, 1 to 2 cc. of a 2 per cent. to 3 per cent. carbolic acid solution, therefore 0.3 grams for the day and have observed favorable results. Other authors, who have used this method experimentally and also in man, have not seen the slightest therapeutic results. The difference in results, especially between the Italian investigators and those of other countries may probably be best explained in that tetanus possibly runs a milder course in Italy than anywhere else in Europe. The mortality from tetanus in Italy is calculated at about 20 per cent., in other countries from 80 per cent. to 90 per cent. I believe, as already mentioned, it to be unlikely, a priori, that in the treatment of tetanus by injections of carbolic acid in severe cases notable results can be achieved.

Before leaving the drug treatment of tetanus another sedative method must be mentioned which possesses prominent importance, namely *narcosis*.

It is unquestionable that there are cases of tetanus in which we can scarcely do without narcosis, in which it even saves life. Among these are cases in which absolute trismus makes it impossible to take food by the mouth. Although, as described in another place, we are in possession of excellent aids, by means of which nutrition may be introduced into the stomach, above all, by subcutaneous injection, it may occasionally be of advantage, at least every two days, to introduce a certain quantity of fluid into the system. As the masseter spasm ceases entirely in narcosis it is very easy to introduce the stomach-tube and allow fluid to enter the stomach. Narcosis is more important, however, in all of those cases of tetanus in which any prolonged manipulation is to be carried out, above all, surgical measures. Subdural infusions, to which we shall refer later on, produce extensor spasm in tetanus, which gives rise to the greatest difficulty in those patients who are not narcotized.

That the anesthetic should only be given by a competent physician with suitable assistants need scarcely be mentioned. The dangers are not to be underestimated which narcosis offers in the case of tetanus; certainly suffocative phenomena may rapidly terminate life. Ether or chloroform may be chosen as the anesthetic; in the choice of a narcotic the condition of the heart and lungs of the patient is to be considered. Regarding the time during which the narcotic is to be administered, this is decided with greatest difficulty. Only observation from case to case decides in such instances. To keep a patient in constant narcosis for days will only rarely be advisable.

In casting a retrospect over what has been said regarding tetanus, we must admit that with all the measures and drugs that have been mentioned, no great results have been attained. The chances regarding the cure of tetanus have only become more favorable since the period at which *specific antitoxin therapy* came into use.

The object of preparing a **tetanus antitoxin** gave rise to particularly great difficulties, in view of the localization of the principal amount of the toxin in the central nervous system. The investigators who busied themselves with this question were clear from the start, that the reaction in the test tube could

not be utilized in regard to the manner of the action of the antitoxin in the human body. The first object was to prepare a pure tetanus antitoxin. For this the method was already indicated. In the beginning of this article, I made an attempt to show the manner in which the organism causing tetanus attempts to produce its own antitoxin, and the scientific basis of the antitoxin theory as well as Ehrlich's theory were described. If these are correct—which I believe to be the case—we have an opportunity of observing in tetanus the wonderful power of nature, for the substance which brings danger and destruction to the animal organism, is capable of bringing about cure and is able to protect other organic beings from the same disease!

Behring and Kitasato arrived at the result, by a great number of animal experiments, by the end of the eighth decade of the last century, in regard to the production of a tetanus antitoxin, so that about the year 1890 the manufacture of tetanus antitoxin en masse could be begun. In producing antitoxin, horses are injected with a dose of toxin which causes tetanus in the animal without inducing a fatal result. In the course of the succeeding weeks the same animals are gradually given larger and larger doses of the toxin by injection. The result of this, is the appearance of large amounts of antitoxin in the blood; the toxin is also found in other fluids of the body but in no other organs except of course the central nervous system and besides in the ovaries. In manufacturing antitoxin for commercial purposes only its presence in blood is to be considered. As the antitoxin is principally contained in the blood serum, this is prepared in a suitable manner from the blood which is taken from horses which have received the requisite treatment, at a particular period.

Three different preparations of tetanus toxin are on the market at the present time. In the following I shall give the scientific details which I have taken from the monograph mentioned several times previously, "Tetanus" by Leyden and Blumenthal.

1. The Behring-Knorr serum manufactured at Höchst both as a solid and a fluid preparation. The fluid preparation is found in the market in small bottles each containing 250 immune units. An immunity unit (I. U.) is equal to 10 toxin units. A toxin unit is the smallest dose of toxin that will kill a guinea-pig weighing 250 grams in from two to four days. In horses and in adult human beings, at once, after the production of the symptoms, the entire contents of the bottle is to be subcutaneously injected; it is advisable upon the two following days to repeat the injection of a bottle of 250 I. U. each day. In children after the diagnosis has been made, half the contents of a bottle is to be injected at once and the other half upon the following day. In the prophylactic treatment of healthy individuals, in whom the outbreak of tetanus is to be feared on account of injury, smaller bottles each containing 20 I. U. are sold. The fluid preparation keeps for some months; the solid preparation an unlimited period. The solid preparation contains the same amount of antitoxin and before injection should have 40 cc. of sterilized water and a trace of sodium bicarbonate added to increase its solubility. The method of injection is the same as in the fluid preparation. The price for 250 I. U. is about 15 marks (\$3.75).

2. The serum from the *Pasteur Institute* is derived from horses and is

furnished in a fluid condition in bottles of 10 cc. without the addition of antiseptics. It retains its antitoxic properties in a cool temperature and in the dark for months. The prophylactic activity of this serum lasts from two to six weeks. The dose for human beings and for larger animals (horses) is 10 cc. in such cases. The antitoxic power of the serum amounts to 1,000,000,000; i. e., to protect a mouse against a simple fatal dose, it is sufficient to use $\frac{1}{1000000000}$ of its weight of serum. For curative purposes 50 cc. to 100 cc. of this serum is to be injected at once or in two doses. The injection is to be made subcutaneously into the leg or the skin of the abdomen or back. For this purpose the skin is cleansed with a 2 per cent. carbolic acid solution or a 0.1 per cent. corrosive sublimate solution. With a syringe which has been boiled for one quarter hour in water and then allowed to cool the injection is made. The point of injection is covered with cotton and some collodion.

3. The *Tizzoni-Cattani* preparation (Merck) contains in every cubic centimetre 80,000 I. U., i. e., an antitoxin amount which will neutralize 80,000 toxin units. A toxin unit, according to this reckoning, is that amount of toxin which will kill a rabbit weighing a kilogram in from four to five days. Commercially the solid preparation is usually preferred. The external peculiarities being the same as in the solid serum of the Pasteur Institute or the solid serum prepared in Höchst; that is: to dissolve the serum in about 50 cc. of sterilized water at about 40° C. (104° F.) is necessary, with the addition of a very small quantity of sodium bicarbonate; 0.1 gram of the solid serum corresponds to a cubic centimetre of fluid serum. As the box contains 5 grams of dried serum the amount of antitoxin is 4,000,000 I. U. In man 5 grams should be injected at once, in horses 2½. Five grams of the serum cost about 37 marks (about \$9).

These are the three principal preparations manufactured in Europe [several just as reliable sera are manufactured in this country]. Unfortunately, these as well as other curative sera (diphtheria curative serum, etc.) which are used in the treatment of infectious diseases, do not retain their properties for a long time and do not show a uniform composition. It was, therefore, a blessing that Prussia decided to erect an Institute which should have for its object the testing of curative sera brought into the market and to give the necessary advice to laboratories that prepare these substances. This Institute was erected in Frankfort on the Main, a short time ago, and is presided over by the celebrated investigator, Ehrlich.

Regarding the mode of employing the antitoxin, up to a few years ago subcutaneous injection was the only method in use. By the use of syringes which had a capacity of from 5 to 10 cc. the amount was injected under the skin of the neck, the breast, the abdomen, the back and the lower extremities in doses of from 5 to 10 cc.

By this method of treatment the results obtained up to now in almost all statistics published are by no means brilliant. The importance of tetanus curative serum for immunizing purposes is unquestioned. The practical consequences which may be drawn from this fact are very great. We cannot agree with those authors who propose to immunize every soldier who is sent to the front during war or every woman with a beginning abortion, or at the

onset of the puerperium, or every new-born child, with tetanus antitoxin. For, on the one hand, it will not be possible for the laboratories to furnish the necessary amounts of tetanus toxin; on the other hand, as we have seen, the total number of tetanus infections, at least in Europe, is a comparatively small one. If, however, in a military or any other hospital, especially during the time of war, and particularly those in which nurslings are treated, a single case of tetanus occurs, the indication is pronounced, besides other general protective measures which are undertaken, to protect all the patients from the danger of contagion by an injection of tetanus antitoxin. Just so, is it advisable in every patient who comes under treatment with a wound contaminated by dirt, immaterial whether tetanus bacilli can be determined in the wound or not, to protect him with an injection of tetanus antitoxin. It can hardly be doubted that if these prophylactic measures are carried out from now on with energy and forethought, tetanus epidemics in hospitals such as have occasionally occurred in the last few years may be prevented, and that the number of individual infections can be decidedly diminished. For this purpose, it is thought necessary that every hospital should have a certain quantity of tetanus antitoxin on hand; for the time which is lost during which the preparation could be procured is usually too great to save the patient into whose wounds tetanus bacilli have entered, and that if he is in the hospital he may have sufficient time before the arrival of the antitoxin to infect other patients.

This fact, that the tetanus antitoxin is frequently injected much too late, is especially the reason ascribed in many cases in which it is used for curative purposes why many cases perish that would have recovered if it had been used early enough; in all of these the injection occurred during the period at which the tetanus toxin was already firmly anchored to the substance of the central nervous system. *To attain favorable results by the antitoxin treatment in tetanus, everything depends upon the fact that it must be employed in a stage in which the toxin produced by the bacteria is for the most part still circulating in the lymph and blood channels.* This toxin may be paralyzed by the subcutaneous injection of antitoxin, prevented from reaching the substance of the central nervous system, and held from entering upon the toxin combination, the actual morbid process. On the other hand, the antitoxin injected subcutaneously does not appear to exert an influence worth mentioning upon the processes occurring in the brain and spinal cord. This is proven especially by the statistics which have been the results of the antitoxin treatment. Lambert recently reported that among 142 cases of tetanus in whom antitoxin was injected there was still a mortality of over 71 per cent. Quite analogous are the results reported by most other authors from the use of tetanus antitoxin subcutaneously.

Shall all these cases of tetanus in which we must assume that the principal amount of the tetanus toxin has already been firmly enchained in the substance of the central nervous system when they reach our hands—and the number of these cases, in view of the long period of incubation which elapses from the onset of the affection up to the period of the first symptoms, will always remain a large one—shall they be excluded from curative serum treatment? Or is it not possible by another method with the antitoxin than that by sub-

cutaneous injection, to disarm the relentless enemy, the central nervous system, of its toxin? These questions during the last few years have been propounded by various authors. The attempt to solve them has been by two methods: first by the direct injection of the tetanus toxin into the cerebrum; secondly, by subdural infusion of the antitoxin into the subarachnoid space.

The method of *intracerebral injection* was invented by two French physicians, Roux and Borrel. It consists in trephining a patient immediately after the appearance of the first symptoms of tetanus, the antitoxin then being directly injected into the cerebral hemispheres. Roux and Borrel, in this method of employing antitoxin in their animal experiments attained far better results than with subcutaneous injections. Great hopes were, therefore, entertained in these results for the treatment of human tetanus and it was employed upon several occasions. Unfortunately these hopes were not realized; for example, according to a collective investigation which Courmont and Doyon recently published, regarding 24 cases treated by the intracerebral method, it was shown that 18 died.

Theoretically, there may be opposed to the Roux-Borrel method, that the antitoxin is not directly introduced into the main seat of the affection, that is into the spinal cord; practically, there is this against the method, that the operation of trephining in a tetanus patient in itself is already a serious undertaking on account of the severity of the operation.

The second new method employed in introducing the antitoxin is *subdural injection*. As this method was only introduced by me a few years ago and but few publications are as yet at hand I may be permitted to enter somewhat more into details in its description. It is well known that in the year 1891 Quincke published his method of *lumbar puncture* and that during the last decade it has been used in most clinics all over the world. It is unquestioned that the method of lumbar puncture has high diagnostic value; but almost as unanimous is the opinion of all authors that the therapeutic value of this method is not very great. It would lead us too far from our theme if I should enter upon an explanation of all the reasons why lumbar puncture is not of great value in therapeutics, besides these reasons are all enumerated in the papers which have been published in the last few years regarding subdural infusion.

The meager results of lumbar puncture in a therapeutic respect and a number of other reasons caused me to enlarge upon the Quincke method somewhat; this was in the winter of 1897. I experimented in numerous animals and immediately in connection with lumbar puncture in infusing various fluids into the subarachnoid space. The results of these experiments I cannot explain at this time; they developed the idea of attempting dural infusion also in tetanus. These experiments were justified upon the basis of various observations; especially this was to be considered that, as the principal amount of the tetanus toxin at the time of the disease in man is firmly enchained in the spinal cord and as this cannot be removed by the subcutaneous use of antitoxin, the chances perhaps might be more favorable if the antitoxin were introduced immediately into the vicinity of the main seat of the affection. Before this method could be used in man, naturally, experi-

ments had to be made in animals. Blumenthal and the author carried out these experiments in goats in 1898 and reported the results at the Congress for Internal Medicine at Carlsbad and in the Hufeland Society in Berlin. The results attained in goats by dural infusion of tetanus antitoxin could not be designated as brilliant; in spite of this, I believe myself justified in advising the method in the treatment of tetanus in man; for, as already mentioned at another place, we cannot compare tetanus experimentally produced in all details with the natural form of the disease occurring in man.

A few words regarding the *technique of subdural infusion*. As simple as lumbar puncture is comparatively, so great are the difficulties in carrying out subdural infusion in tetanus. To introduce the needle between the third and fourth lumbar vertebræ and to reach the subarachnoid space the patient must be placed in the proper position, that is he must be placed upon the side completely horizontal to the bed, the back well bent and the abdomen strongly retracted. To produce this position in tetanus is impossible on account of opisthotonos; on the contrary, even the attempt to place the patient upon his side, disinfection, etc., all these manipulations usually produce an exacerbation of the spasmodic attacks. For these reasons I believe it justifiable to give the patient suffering from tetanus, before the operation is attempted, a single large dose of a narcotic (best a mixture of chloral hydrate with morphia) or to keep him under an anesthetic. This facilitates the slight and harmless operation. The injection of antitoxin then occurs in the usual manner; 5 to 10 cc. of the cerebrospinal fluid is allowed to flow off from the Quincke needle; while a few drops are still oozing, the outflow opening of the needle is attached to the antitoxin syringe (to prevent the entrance of air into the subarachnoid space) which holds 10 or 20 cc. and with the least possible pressure, minute by minute 1 to 2 cc. are injected. After the injection is finished the syringe armed with the needle is allowed to remain for one to two minutes at the point of injection, and is then removed with a single effort; the opening is closed with some collodion.

What quantities of antitoxin are to be introduced into the subarachnoid space for curative purposes cannot as yet be definitely determined. Upon the basis of the experiences which we have gathered with other fluids in subdural infusion, the following may be said, that many of them in the $\frac{1}{10}$, $\frac{1}{100}$, even $\frac{1}{1000}$ part of what is usually given by mouth or subcutaneously show an action on the organism if they are injected into the subarachnoid space. Nevertheless, in the case of tetanus especially, in view of the firm anchoring of the toxin in the substance of the central nervous system, I would not advise giving a smaller dose of curative serum by subarachnoid injection than that used for subcutaneous purposes.

Still another remarkable condition must be finally mentioned which occurs after subdural injection of antitoxin as well as of other chemical substances, for example, solutions of iodine, which is noted a short time after the operation and is almost constant, namely, a rise in temperature amounting to a degree and a half to three degrees and more. This phenomenon probably depends, as has already been mentioned elsewhere, upon a chemical irritation of the heat centre. Inside of twenty-four hours after the injection it always disappears and does not give rise to any deleterious effects, in fact, we have

never seen any disturbing secondary phenomena after subdural injection of tetanus antitoxin.

In the First Medical Clinic in recent years there was an opportunity in two cases to perform subdural infusion of tetanus antitoxin; the permission for the use of these cases was given by my chief, Prof. v. Leyden, who showed marked interest from the onset in my endeavors to develop a therapeutic method from subdural injection. Prof. v. Leyden reported these cases minutely; the first case he showed in the summer of 1899 to the Charité Society, the other at a meeting of the Society for Internal Medicine of Berlin in 1901. I may, therefore, refer to these publications and need not repeat the accurate clinical histories. I should only like to emphasize here, that both of these cases treated by subdural injection belong to the severest forms of tetanus. The one occurred in a patient showing the puerperal form, the first symptoms appearing ten days after an abortion, an incubation period of one to eight days according to the statistics of various authors shows a mortality of 91 per cent.; the mortality of tetanus puerperalis is estimated by some even at almost 100 per cent. In this case, in view of the total symptom-complex, a very unfavorable prognosis was to be expected, and I practised two subdural injections; upon the sixth day after the appearance of the disease 10 cc. of Behring's tetanus antitoxin (equals 1 gram of solid substance) was injected into the subarachnoid space of the patient; upon the same day there was also administered 2 grams of Tizzoni's serum subcutaneously, as we desired to leave no remedies untried that might offer a faint possibility of cure. As the clinical symptoms did not improve decidedly after the first subdural infusion, two days later $1\frac{1}{2}$ grams of Behring's curative serum (in two parts each containing $\frac{3}{4}$ of a gram) were again injected into the subarachnoid space. From this day on the condition of the patient improved steadily; four weeks after the appearance of the first symptoms, the patient left the hospital cured.

A more severe case but even more valuable regarding the use of subdural infusion of tetanus antitoxin was the second in which this method was used. A hostler aged twenty-two, in May, 1901, was admitted to the First Medical Clinic with the symptoms of severe tetanus. How long the period of incubation had lasted in him could not be ascertained, as the patient could not remember suffering from trauma, and upon the most careful investigation no signs of an injury could be ascertained. The prognosis of the case was, therefore, looked upon as almost entirely hopeless, as upon the second day of the disease he showed a temperature of 104° F. Upon the third day of the disease, I injected into the subarachnoid space 5 cc. of Behring's fluid antitoxin (corresponds to $\frac{1}{4}$ gram of the solid preparation). The temperature upon the same day fell to 101.3° F. and upon the next day to 99.2° F., an effect which v. Leyden designated as "life saving." All of the other symptoms of the disease after the dural injection decreased decidedly in intensity; as a slight increase could be noticed two days later, I gave the patient the same quantity of Behring's serum by subarachnoid injection. The improvement in the patient continued without further disturbance. In the course of two weeks he was able to leave the hospital cured.

Similar favorable results have been obtained by subdural infusion with

tetanus antitoxin in other Clinics. Above all, the investigations of the French author, Sicard, are to be mentioned, who developed the same method experimentally in France about the same time.

Regarding the use of subdural infusion in man, Leyden and Blumenthal in their monograph have collected 9 cases of which 3 recovered (among the 6 cases that died were 3 cases of tetanus neonatorum that can hardly be compared with the cases of tetanus in adults). (To the 3 cases cured 4 others must be added, 1 from the clinic of Jaksch, 1 from the clinic of Kast, the last mentioned case of von Leyden and a new one not yet published from Leyden's clinic.) Therefore, in two-thirds of the cases in adults treated by subdural infusion, recovery has occurred, a remarkable result in view of the otherwise unfavorable statistics, so that von Leyden has proven the method of subdural injection of antitoxin in tetanus as superior to all other forms of treatment.

The antitoxin treatment of tetanus is one of the most beautiful fruits obtained from the blooming tree of scientific investigation at the close of the last century and harvested for the new century.

Let us hope that by this method of treatment the number of cases suffering from tetanus as well as the mortality may be more and more decreased and that after a few years this affection can no longer be classed with the group of the almost incurable affections.

[See also Serum Therapy, page 909.]

HYDROPHOBIA, RABIES

By F. PENZOLDT, ERLANGEN

THE clinical picture of human *hydrophobia* also called rabies, lyssa, etc., unquestionably belongs to one of the most terrible and sad conditions which occur in the practice of the physician. The suddenness, the unexpected result of the dangerous injury, the fear of the outbreak of the affection, assisted by the uncertainty of the often long period of incubation, the frightful, painful suffering itself, and finally the impossibility of cure after the disease has once developed—all these conditions justify the expression with which this article begins.

Fortunately this terrible disease is rare in many countries. Many physicians, who have large practices never see a case in their entire professional career. But in spite of its rarity, hydrophobia has great practical importance. In this respect, it is similar to most acute cases of poisoning. The physician must be in a position, immediately after a suspicious injury produced by a bite, to at once do everything in his power to make a positive diagnosis of the disease in the animal and to prevent the appearance of the affection in the human being. For this purpose the physician must be acquainted with all necessary details regarding the pathology and therapeutics of hydrophobia. To this must be added that, opposed to the numerous legends with which this peculiar affection in animal and man is surrounded, the physician is the recognized exponent in this instance of our clear scientific views regarding the disease. The physician has the honorable and important duty, as in other hygienic questions, so in this, to set the popular mind aright.

ETIOLOGY

The Nature of the Affection.—This may be characterized briefly in the following sentences: Hydrophobia is an infectious disease occurring in wounds due to a morphologically unknown infectious cause; however, one in which the pathogenic properties are well recognized, usually contained in the saliva of a rabid animal, which after a variable period of incubation, commonly lasting weeks, gives rise to a disease in the central nervous system in which histological changes occur, with severe irritative symptoms (spasms in deglutition, respiration and other reflex phenomena, delirium) and terminal paralysis which mostly runs a fatal course in from two to four days.

The cause and manner of development of hydrophobia, upon the basis and with the aid of experience with which the facts gathered from experiments have been determined is known to us with sufficient exactness. Even if we do not know the manner and form of the contagious principle as yet, there can

be no doubt that it is due to an animate infectious agent. This only enters the healthy body, almost exclusively, by the saliva as the result of a bite by a rabid animal. That a wound, due to any other cause may be infected by saliva or nerve-substance of an animal sick of hydrophobia is possible and has been experimentally proved. In practice, however, this eventuality is very rare and need hardly be considered.

The opinion which still exists and is widely distributed among the laity of a spontaneous development of the disease—in the dog, due to great heat, thirst, unsatisfied sexual desires—as in other infectious diseases, so also in hydrophobia is absolutely untenable, and must be relegated to the domain of fairy tales. Such superstition, however, has new nourishment supplied to it by the quite frequent cases in which, in a district apparently free from hydrophobia, the disease suddenly appears among dogs. If now, as in the case of most infectious diseases, we do not succeed, in the individual case, in determining the source of infection, our knowledge is quite sufficient to teach us that the autochthonous development of the disease is quite impossible, for it has never been possible to produce hydrophobia in an animal by the conditions mentioned above.

The possibility of infection by products remaining a longer period in the earth or by fomites may be neglected, the chances being extraordinarily slight. For *air* and *light* destroy the virulence of the lyssa virus very rapidly in days, *moisture* and *decomposition* certainly diminish it decidedly in weeks, so that a retention of the infectious germs in the earth, as in the case of tetanus, need not be considered in the case of hydrophobia. Thus the development by transmission from individual to individual only remains and, on account of the fixed character of the contagium, by wounds from bites.

The opportunity for propagation of infection in the animal economy is always present, as almost *all mammals*, wild as well as tame, may be affected by hydrophobia. Besides dogs, the disease occurs in wolves and foxes, in cats, in horses and mules, cattle, sheep, goats, pigs, deer, in martins, and badgers, as well as in the notorious carriers of infection, rats. As the most of these animals bite each other the opportunity for transmission of the disease is frequent enough. As in many of the previously mentioned animals, the affection is not known as in the case of dogs and valuable domestic animals, because they hide themselves as soon as they become sick, it is readily understood that hydrophobia may propagate itself in an unknown manner until a dog is bitten and then the affection distributes itself among dogs. In cities, dogs are principally infected by cats and rats; in the country also by wolves, foxes, martins and other animals. The long period of incubation is naturally also responsible for the fact that the infection is often carried to quite distant places and then suddenly appears there.

Although almost all mammals are capable of distributing rabies, dogs are responsible in nine-tenths of the cases for the transmission of the affection to man. In the other one-tenth, about one-half (therefore one-twentieth) is due to cats, for the remainder other animals are responsible (particularly wolves, ruminants, and the solidungula). Persons affected by hydrophobia are only the cause of the affection in one per thousand.

The nature and form of the infectious agent, as has already been men-

tioned, is not definitely known. At least none of the investigations directed to this point, from the oldest and most untenable of Hallier up to the newest, those of Bruschettini, and others carried out with the best methods, have attained general recognition. This is equally true of the investigation to prove a bacterial organism, as also those that have searched for a chemical toxin produced by pathogenic microorganisms. The pathogenic properties of the infectious agent have, however, been determined with exactness by experiments, which in a measure supply our insufficient morphological knowledge. Experimental investigation has become particularly successful since the method discovered by Zinke in 1804, showing the transmissibility to rabbits, came into general use. (Galtier, 1879.)

Numerous fluids of the body and tissues have been recognized as the *seat of the infectious principle*. Above all, the *saliva*, and the salivary glands, have long been known as the carriers of the contagious principle. This has also been found to be true of the tear glands, pancreas, the mammary glands, the milk, testicles, adrenal bodies and urine, however, the spleen and the liver have given negative results; the lymph-glands doubtful ones. The question is also undecided regarding the muscle, while it has been definitely determined that the blood cannot be looked upon as infectious. Nor has a placental infection been proved. The contagious principle is contained in largest amounts in the *nervous system*. The opinion formerly expressed, became a certainty by the fundamental investigations of Pasteur (1881). While the peripheral nerves are not constantly virulent, the brain and spinal cord, the white as well as the gray substance, and especially the medulla oblongata develop the disease, if the correct method of inoculation is practised. Pasteur's method depends upon preparing an emulsion consisting of sterilized bouillon (or physiologic salt solution) in which the medulla oblongata of an animal obtained from a case of hydrophobia is pulverized; this is injected, with a syringe, the needle being curved, under the dura of an animal after trephining, and especially in an animal that is very susceptible to rabies (dog, rabbit, guinea-pig). The important principles included in this method, the positive virulence of the lyssa brain on the one hand, and the positive susceptibility of the lyssa toxin upon subdural injection on the other hand, were the foundations for the great rise in our comprehension of the pathology of hydrophobia in the two last decades of the nineteenth century, and also of the immediate brilliant advance of experimental therapy, the prophylactic treatment of hydrophobia.

The *points of entrance* and accordingly the *variable susceptibility* of the infection have become known to us by the method of inoculation based upon the constant virulence of the central nervous system. Apart from the almost certain development of the disease by the injection of a cerebral emulsion subdurally, into the optic nerve, tympanic cavity, serous cavities, etc., it is of decided importance that the injection of the toxin into peripheral nerves and into muscles gives positive results, while when injected in the veins and into the subcutaneous tissue and still more into the skin uncertain results are obtained. The latter is also true of the application of a cerebral emulsion to the "undamaged" mucous membranes of the mouth, nose or conjunctiva, respiratory and urinary passages, as well as especially to the gastric mucous

membrane. In this connection, it must perhaps be considered that in a positive result the danger of injury to the mucous membrane can never be entirely excluded, whereas conspicuously many negative results, especially one also with meat and saliva in a human being (Ducroix) are at hand.

In all of these experimental infections it is to be observed that unquestionably the amount of the introduced infectious material is also of influence.

The *strength (virulence)* of the infectious product is dependent upon very varying conditions. As a measure, besides the success of inoculation, the production of the disease in general and also the *duration of the period of incubation* may be considered. Whereas the infectious material taken from a dog that has accidentally contracted rabies, "*street hydrophobic virus*" of Pasteur, in the subdural inoculation in rabbits gives rise to hydrophobia upon an average in fifteen days, the infectious product taken from rabbits that have been inoculated into rabbits subdurally, the "*passage virus*" of Pasteur, produces the disease in a briefer period, and, finally, always after six days. The incubation does not fall below this period, i. e., this is the strongest grade of infectiousness of the principle. Thus, *an increase of the virulence* may be obtained.

Attenuation of the virulence is accomplished in a similar manner as its increase, by continued transmission from rabbit to rabbit, from dog to dog by inoculation (also in monkeys). A decrease in toxicity is attained if the brain-emulsion of rabid animals is mixed with the blood serum of animals that have become immunized in a natural manner (for example, pigeons) or of artificially immunized animals (dogs, rabbits), further, if it is mixed with gastric juice.

The virulence ceases with varying rapidity, but only after some hours by the influence of many of the well known *disinfectants* which are applied to wounds in a concentrated form. Chlorine water appears to act most intensely. Of other influences which diminish the virulence or cause it to disappear, heat must first be mentioned (at 50° C. in one hour, at 60° C. very rapidly), *dilution*, *drying* (in from ten to fifteen days from the medulla oblongata), *light* and *oxygen*, whereas cold and decomposition act but very slowly.

Regarding *susceptibility to the infection*, it may be remarked, in general, that almost all persons are susceptible. However, not all persons that are bitten by rabid animals are actually attacked by hydrophobia. It is almost impossible to give exact reports by statistics regarding the mortality, above all, because it is so difficult, in every case of a bite to determine with certainty that the disease was present in the animal. In a compilation, which only includes the cases determined by veterinarians, there is a mortality of about 50 per cent., whereas in bites from animals in whom there was only a suspicion of hydrophobia there was a mortality of but 15 per cent. to 20 per cent. *Sex* and *age* do not show any variation in regard to susceptibility.

The danger of contracting the disease is influenced decidedly by the extent and seat of the infecting bite in the individual. Large, deep and numerous wounds are certainly more dangerous, therefore, the estimated mortality in bites from wolves amounts to about 60 per cent., even in some cases to 90 per cent. of patients. Regarding the location of a bite, those in the face are most dangerous (according to statistics 88 per cent.), than upon

the hand (67 per cent.), less dangerous upon the arm and the lower extremity. The reason for this condition may be looked for primarily in the fact, that in uncovered areas the infected saliva reaches the blood in greater quantity than in those areas protected by the clothes. But the richness of the face and hands in nerves, as well as the proximity of the brain to the face, may also be of influence.

Regarding *the danger, in general, in being attacked* by hydrophobia, the distribution of the infection in animals and man as shown by statistics gives some points of support, although by no means reliable ones. The height of the morbidity figures is determined not by the actual condition, but by the accuracy of the statistical accounts. This is, however, very slight in some positive hydrophobia countries. For this reason, but few figures taken from the accurate statistics of the German Empire are to be mentioned. In the year 1897, there were attacked by hydrophobia and died, 905 animals (among these, 106 cattle) and 10 human beings; there were killed, on account of being suspicious cases of hydrophobia 2,180 dogs. According to the same statistics, there was certainly an increase of the disease in Germany toward the end of the nineteenth century. It is, however, further certain that a decided distribution only occurred in those parts of the country which border upon Russia and Austria. Thus, in 1896, among the dogs reported as rabid, 96 per cent. occurred in East and West Prussia, Posen, Silesia, and the Kingdom of Saxony, and only 4 per cent. in other parts of the empire. There can, therefore, be no doubt that the disease is principally introduced by our eastern neighbors. In general, it may be said, that the danger *ceteris paribus* is greatest where dogs most abound, and where the dog police is insufficient or not thoroughly experienced. But the distribution in the eastern part of our country teaches that even with good precautionary measures the danger of introduction is constantly great.

PATHOLOGY

Anatomical Changes.—The anatomical changes in animal and man are so slight that *macroscopically* they show absolutely nothing that is characteristic. At the autopsy, at least in the dog, the fact that no food is present in the stomach, but that on the other hand, indigestible substances, such as earth, straw, grass, wood, etc., are present is in favor of hydrophobia. But the absence of these substances is not actually against hydrophobia. If the opportunity of swallowing such material is absent in the dog, or if deglutition is impossible, on account of paralysis, the absence of this proof is readily understood. But this condition may also be absent in rabies with a sufficient power for swallowing indigestible substances, as was shown by an observation of my own. In man, naturally, this finding is always absent.

The absence of gross anatomical changes are only insufficiently compensated by the advances of histological investigation. In referring to the description of the histological findings in the accurate description of hydrophobia by Högyes, in Nothnagel's Handbook, a few hints must suffice for the present. The disease consists in an acute inflammation of the central nervous system, especially of the spinal cord. The nerve-cells, especially those of the

anterior horns of the gray substance, show degenerative changes, with a cloddy condition of the chromatin in the cell-body and nucleus. Besides, a plentiful leukocyte infiltration is present in the spinal cord of the perivascular and pericellular spaces, which according to Babes, are said to be characteristic, in forming a focal collection, the so-called rabies nodules. As, however, the determination of these changes requires time and much experience, the diagnosis at the autopsy had better be made by the previously described subdural inoculation of rabbits.

SYMPTOMS

In the description of the symptoms of hydrophobia, we must mention those briefly occurring in dogs and rabbits as well as those which are observed in man. The recognition and judgment of a hydrophobia infection in man is facilitated by knowing the symptoms in the animal, and for this reason it is of great importance.

In the dog, *a period of incubation*, upon the average sixty days, is assumed if the disease is due to an accidental bite, whereas in a subdural inoculation the period of incubation amounts to but from ten to fifteen days. Without distinct signs, the initial phenomena, which last from one to three days appear: with increase of temperature and of sexual desire, irritation and a varying condition, at one time sad at other times tendency to play, develop; the symptoms are as yet by no means characteristic. This is of great practical importance, for the disease in this stage is already contagious. The dog that in my case was the source of infection, shortly before biting, had played with other dogs and as he passed by me, he showed no conspicuous symptoms and upon the following morning took his usual amount of food and even the veterinarian did not observe symptoms at this time.

Again without a noticeable transition the *actual symptoms* of the disease, which may show themselves in the form of a *raving*, *quiet*, or *paralytic* form, appear. In the raving form, there is observed: complete change of disposition, marked tendency to bite, meaningless temper, restlessness, unwillingness to eat, swallowing of indigestible substances, hoarse voice, reddened eye, and gradual increase of paralytic phenomena in the hind legs, death mostly upon the fifth or sixth day. The quiet form is characterized by the shorter duration or the absence of irritative symptoms, the inability to bite due to early paralysis of the lower jaw and the presence of paralytic phenomena in general. In both forms, in artificially produced cases occasionally recovery is observed, so that this must be looked upon as possible even in accidental infection in dogs.

In *rabbits* the symptoms after inoculation of street rabies usually appear between the twelfth and the twenty-first days. They usually correspond to the quiet form of rabies in the dog, although irritative conditions are observed (unrest, trembling, jumping, crying upon irritation, etc.).

The *symptoms in man* occur after a varying *period of incubation*, a minimal duration, that observed in my case, of eleven days may be assumed, as in cases of a shorter period of incubation the diagnosis has probably not been positive. The reports regarding the maximum period, if these are longer than

a year, must be accepted with caution. Most likely in the cases in which the period of incubation has been said to have lasted for many years, apart from diagnostic errors, it can never be maintained with certainty whether a renewed infection in the period between, that is between the first bite and the appearance of the disease, has occurred (an unnoticed bite, injury or contagion by licking a wound). An average determination of the period of incubation, on account of the great variation, is of no value. It is sufficient to know that in about four-fifths of the cases, in the second month, almost nine-tenths of the cases inside of three months after the infection, show symptoms. In children and in very pronounced injuries (wolves), the period of incubation is shorter upon the average, as the virulence, as has been experimentally proved, has an influence upon the period of incubation, upon the infectious material that has entered, whether the wounds are superficial or deep, whether the bite has occurred through clothes or upon bared areas, perhaps also dependent upon the nature of the animal that has produced the wound.

The *healing of wounds*, naturally, excepting those which are treated by strong cauterization, as well as the very extensive ones, takes a quite normal course. For this reason most wounds have cicatrized before the appearance of the disease. Anesthesia and hyperesthesia at the point of the wound, paresthesia and pain in the affected part of the body have frequently been observed. But it is not improbable that these phenomena, inasmuch as they occur early, are of a more psychical character. If they occur toward the end of the stage of incubation, they may be looked upon as prodromal symptoms.

The *true clinical picture* may show itself in three forms, the most frequent being the *raving form*, the least frequent, corresponding to that called in animals known as *paralytic rabies*, and finally also in an *abortive form*, influenced by protective inoculation. These forms, especially the first, may be divided into a *prodromal stage*, into a *stage of spasm* or irritation and into a *paralytic stage*.

In the *prodromal stage* the previously mentioned subjective phenomena, in the area of the bite and in its surroundings that have already been mentioned are observed. To this may be added, local objective changes, reddening and swelling of the cicatrix; in my case, painful enlargement of the adjoining anatomical glands, tremor of the affected part of the body, in bites upon the face, frequent attacks of sneezing, or in my case in which the eye was injured by the nose of the dog, a painful redness and swelling of the eye which disappeared in some hours, resembling a beginning ophthalmia. The mental condition varies, usually it is sad (*stadium melancholicum*), even without the patients having an idea of the fate that is in store for them, more frequently they are irritable, lively in spells, occasionally even with actual disturbances of the mind (delusional ideas). Suggestions of spasmodic conditions by sensory irritation, for example, impressions from bright light, occur; rises in temperature are said to occur; frequently the temperature, however, does not rise above 100° F. in the rectum, as for example in the case observed by me. Regarding the duration of the prodromal stage, nothing definite can be said, as the onset is insidious and gradual and only the end of the period may be somewhat more plainly defined. We will not be far from the truth if we assume that from two to three days is the average.

The onset of the *spasmodic stage* may be reckoned from the first well-developed spasm in deglutition or respiration. Especially in an attempt at drinking (in my patient not in drinking from a cup but shortly thereafter in drinking from a transparent glass) the first well-developed *spasm of deglutition* appears (hydrophobia) and with this the diagnosis at once becomes clear. The sensation of constriction of the neck, combined with terrible fear and difficulty in respiration, not only follows an attempt at drinking, but every irritation with increasing frequency and severity (light, sound, cold, touch, blowing, etc.). Whereas the respiration becomes irregular, suspended, sighing, forcible, spasmodic, there are added to the local spasms of deglutition and respiration, tremor and general reflex convulsions. Reflex irritability is increased in general (skin, tendon and muscle reflexes). To this, great unrest to actual maniacal attacks is added, in which the mind, though normal up to this point, gives way. Tendency to bite occurs, but this is not of regular occurrence, this tendency is rarely directed toward others, usually to his own person. The heroic deed of a smith bitten by a rabid dog, who is said to have fastened himself to his anvil before the development of his disease to protect those surrounding him from his bites, as beautiful as it appears must be looked upon as entirely superfluous. The *profuse salivation* is very characteristic. Whether acetonuria is a constant symptom, must be determined by further observation. The temperature gradually rises more and more with an increased cardiac and respiratory frequency, at other times this is not marked. Toward the end, however, hyperpyretic rises in temperature are frequent. The duration of this stage, counted from the first distinct spasmodic attack, is usually two to three days. Death may occur in this period.

The *paralytic stage*, which according to what has just been said need not always be present, consists in the cessation of all spasms and irritative phenomena, even swallowing becomes possible again; further, numerous local hemiplegic or paraplegic or general muscular paralyses appear which finally terminate the life of the patient. This stage lasts but a few hours, up to eighteen.

In regard to the *paralytic form* of lyssa we may be brief. The symptoms of this much more uncommon form of the disease are upon the average those observed in the quiet form of rabies of the dog, which have already been mentioned as well as in the symptoms in the last stage of the common form. The initial symptoms resemble ordinary hydrophobia, the irritative phenomena consist in tremor and spasm, usually first in the wounded part of the body, thence soon spreading and distributing themselves to the muscles of the entire body until paralysis occurs. The duration of the affection is somewhat longer than in the common form and may last seven days. The reason why paralytic rabies occasionally occurs is assumed to be in a much more powerful infection, partly in a predisposition of the individual (individual cases occur in neuropathic or epileptic individuals).

Finally, the milder, *abortive form* of rabies. This is occasionally observed after protective inoculations. It consists of a prodromal, eventually also of milder irritative phenomena and of the stage of general paralysis. In very rare cases recovery is reported in inoculated persons after the appearance of

mild symptoms (fever, pain in the wound, difficulty in swallowing, paralysis of an extremity). But in these cases the positive proof by the inoculation of the saliva in animals is absent so as to determine whether rabies was actually present.

Regarding the manner and mode of the *development of the clinical picture by infection*, we are in possession of partly accurate but for the most part only of hypothetical views. The track of the infectious product is toward the central nervous system by means of the nerves as has been determined by experimental investigations. It is, however, likely, according to the positive result of intravenous injections, that the infection may reach the brain by means of the circulation. In the central nervous system, it is probable that the infectious product increases and by means of the nerves and perhaps also by the circulation, it affects the peripheral parts (salivary glands). That the previously described changes in the brain and spinal cord are the cause of the clinical symptoms is possible. It is more likely that a hypothetical toxin developed by a hypothetical pathogenic agent, gives rise to the severe, acute course. For the clinical picture has the greatest similarity to a severe intoxication.

DIAGNOSIS

The diagnosis of rabies after it has developed, as a rule, does not give rise to difficulties, if the points are taken into consideration which were mentioned in the etiology of the affection, in the description of the disease in animals, and the course of the affection in man is considered. Among the symptoms, the spasms of deglutition and respiration are the characteristic ones. Attention is called to the fact that these may be produced, as a rule, by the mere blowing of the breath upon the skin. But the test by drinking a clear fluid, is also worthy of observation. The possibility of mistaking hydrophobia is especially marked in those cases of so-called *lyssophobia*, tetanus hydrophobicus, delirium tremens, and similar mental disturbances, particularly if a bite has preceded the development of the condition. Lyssophobia in hysterical persons may be recognized from the accompanying phenomena, the absence or brief incubation, the early recovery. Probably most cases of recovery from hydrophobia have been cases of this kind. *Hydrophobic tetanus differs*, by the briefer period of incubation and the simultaneous trismus. In the different varieties of *delirium*, especially of *delirium tremens*, the delirium at the onset and during the course is the prominent symptom.

PROGNOSIS

To discuss *prognosis*, in the usual manner, after the clinical symptoms have been described, is of little value in hydrophobia as this is only a repetition of what has already been said of the disease and of what must still be said in the therapy.

THERAPY

The treatment of hydrophobia may be divided into an effective therapy, *the prevention*, which again consists of the control of the infection and in the prevention of the outbreak of the disease, as well as in an inactive one, the treatment of the developed disease.

The measures for the prevention of infection may consist in a diminution of the danger of infection, especially that brought about by the dog, in general, and in the prevention of an epidemic of hydrophobia in special.

Limiting the number of dogs, especially the homeless ones, has been brought about by the dog tax. This should be high (\$4 to \$5) and should not, as is common in some countries in which danger of great infection exists, be low. The laws combined with this should be strictly enforced; the dog should carry the tax check in plain view around his neck, and this should also contain the name and residence of the owner; in case the dog is found without this, he should be treated as "homeless." Besides, everywhere other laws should make it very difficult to keep dogs; prohibiting taking dogs into public places, allowing the dog to run around at night; a muzzle to be worn by all dogs. Finally, the question of immunizing the dog should be brought up. That dogs may be made immune by Pasteur's method of inoculation is certain. Whether the immunity is a permanent one has not yet been determined with certainty. The difficulty of the process has been a hindrance up to now, at least for the general introduction of the practice.

In the *outbreak of an epidemic* of hydrophobia, there should be an international duty to inform the countries or districts adjacent to the focus of the disease. The laws for the German Empire have been described in the Cattle-Plague Law of May 1, 1894: Duty of the owner to report the case, veterinarians, etc., before the police interfere; destruction or positive isolation of the rabid animal, or the suspicious animal; if other animals or human beings have been bitten by the suspicious animal, isolation and observation is to be enforced. By the police, or the district veterinarian, the destruction of the animal that has hydrophobia as well as of all animals bitten by it, with the exception of horses, cattle, etc.—these are to be observed; in a mere suspicious case an eight-day observation also of the dog; general prohibition for dogs amounting to 4 kilometres in the vicinity of the district in which the sick dog has been, that is, all dogs are to be fastened to chains or led upon a leash with a secure muzzle, killing of all homeless dogs as well as of cats. Especially important, upon the eastern borders of the realm would be a strict control of dogs running over the border as well as the sale of dogs in the district in which the epidemic is prevalent.

The success of all these preventive measures, which have only been reported in the main, depends naturally not only upon the law but upon its exact enforcement; this has been very satisfactory in Germany regarding the larger neighboring States, in that in Germany there is one rabid dog for every hundred thousand inhabitants, in France 1 to every 30,000, in Austria 1 to 27,000 and in Hungary 1 to every 15,000.

The prevention of the outbreak of hydrophobia must be attempted by thorough cleansing of the wound and destruction of the poison. Most useful for this purpose is a rapid cauterization with the actual cautery. Animal experiments have taught that this only succeeds with certainty in arresting the disease if the cauterization occurs in the first few minutes after infection has taken place. With every hour lost the results become more uncertain, and disappear entirely after a day. It is, therefore, advisable at once with a glowing hot instrument, no matter what may be at hand (a needle, knife);

to cauterize the wound thoroughly. This should even be attempted after some hours, even after the second day, as it may be hoped that by the destruction of the virus, which has remained in the wound, at least the chances for a protective inoculation may be improved, causing a prolongation of the period of incubation. A thorough cleansing and allowing the wound to bleed is to precede cauterization. If at hand, a 1 per cent. solution of corrosive sublimate or other disinfectant or caustic remedies are to be used. In epidemics, the public should be instructed and in villages, for example, the sublimate solution should be kept by some official for immediate use, even without the presence of a physician. According to statistics it may be assumed that among those that are cauterized twice as many escape as among those not so treated.

Protective inoculation *with attenuated lyssa virus, given at the proper time after infection, prevents the outbreak of hydrophobia in the greatest majority of cases.* As an experimental foundation of the method the following trials of Pasteur are to be considered: If dogs are infected subdurally with "street rabies virus" and spinal cords which have been subjected to drying for from fourteen days to one day and these are successively injected so that upon the following day they take the entire series, the greatest number of dogs will be saved.

Protective inoculation based upon this and other experimental results may be carried out with some individual modifications but in principle with the same procedure. To give a detailed report describing the methods is not within the scope of this article. The treatment is carried out in institutions especially designed for this purpose and can only be properly used in them. Such institutes are found in Berlin, Vienna, Budapest, Paris, Turin, Milan, Naples, Palermo, St. Petersburg, Moscow, Odessa, New York, and many other places. The physician need only understand the process in general, hence the following remarks will suffice:

From a rabbit that has perished from rabies (fixed virus) an emulsion of the prolonged cord preserved in glycerin is injected daily into one or more rabbits subdurally. In this manner, after the usual period of incubation, cadavers are obtained daily of rabbits dying of rabies, and by autopsy and inoculation into healthy animals it must be proved that they have actually died of hydrophobia. In these rabbits the spinal cord is aseptically removed and placed in a glass the floor of which is covered with pieces of caustic potash, kept at a temperature of from 20° C. to 22° C. in the dark and hung up to dry. By the process of drying, the amount of poison contained in the cord diminishes from day to day. Now a piece of the cord thus treated amounting to a centimetre is cut off, crushed in bouillon and injected, 1:3 cc. into the lower abdominal region. The process varies according to the kind of bite, i. e., according to the danger in that only a brief period of incubation is to be expected. Pasteur's method in wounds of the head was, for example:

	1st day	each	3 cc.	of	14-11	day-old	cord.
	2d	"	"	3	"	"	10- 7 " " "
	3d	"	"	2	"	"	6 " " "
	4th-5th	"	"	2	"	"	5 " " "
	6th	"	"	2	"	"	4 " " "

7th day each	1 cc. of 3 day-old cord.
8th " "	2 " " 4 " " "
9th " "	1 " " 3 " " "
10th-11th " "	2 " " 5 " " "
12th-13th " "	2 " " 4 " " "
14th-15th " "	2 " " 3 " " "

and so on up to the twenty-first day, but never over 2 cc. of a three-day-old cord.

In bites of the extremity especially at the onset a slower process is employed. On the other hand, very probably, if only a brief period of incubation is to be feared (in bites from wolves upon the head for example) larger doses of the emulsion are given, more rapid, virulent injections are used and finally also a two-day-old and a one-day-old or quite fresh cords are injected. Among modifications of the attenuation process the dilution method of Högyes is the main one.

The *duration* of the treatment amounts, upon the average, to from two to three weeks, but in injuries that have a bad prognosis this should be extended to four weeks or even longer.

In judging of the *success* of protective inoculations, statistics are to be used with certain limitations. This much is certain that the success is slight in the cases in which the period of incubation is a short one. Immunization by inoculation requires a certain time, and this can no longer be attained if rabies appears early, similar to the case of vaccination in an outbreak of variola which no longer prevents the disease if it is carried out eight days after the infection has occurred. It is, therefore, justified in this limited sense as for instance, if in statistics amounting to almost 43,000 cases, as is done by Högyes, the fatal cases that died during treatment or inside the first month after the bite had occurred are excluded from the calculation. Enough cases still remain that would have terminated fatally without treatment for, as we have seen, about four-fifths only show the disease in the second month after the bite. In comparison with the ordinary bad prognosis, the result is still brilliant enough if after the limitation previously mentioned only 0.57 per cent. of the inoculated individuals died. But even if those are included that die during treatment the mortality does not exceed 2.7 per cent., and when it is remembered that the general mortality in the minimum is 15 per cent. but that this, on account of including all suspicious cases, is much too small—for example, after bites from wolves the mortality amounts to from 60 per cent. to 90 per cent.—there is certainly not too much claimed if the number of those dying, in spite of protective inoculation, is estimated as the tenth part of those succumbing to lyssa without treatment. The main requirement for success is an immediate treatment after the bite. A compilation of 5,785 cases from the Institute in Odessa shows a mortality of 0.56 per cent. in those coming under treatment in the first week, whereas the mortality rose to 3 per cent. in those in whom the inoculation was only begun in the third week. Besides, it is to be hoped that with time we shall succeed in saving even those cases with a most unfavorable prognosis by a more rapid and energetic procedure.

The treatment of developed rabies compared with the splendid facts of

preventive therapy is still as hopeless as formerly. The cases not prophylactically treated may be looked upon as absolutely fatal. This is probably the only acute disease which offers such an unfavorable prognosis but it at least leaves a ray of hope reflected by the observations during protective inoculation that symptoms of hydrophobia have disappeared of themselves or by a continuance of the treatment that the diagnosis "hydrophobia" in all of these cases was not beyond question. Perhaps we will still succeed, as was maintained in one case, to influence the developed disease by attenuated lyssa virus or by immunized blood serum.

Until this goal is reached we must content ourselves with a *symptomatic therapy*. To diminish the terrible, irritative condition, quiet, warmth, darkening the sick room must be employed. Narcotics must be utilized, among these chloral hydrate, as an enema, deserves the most confidence. Large and frequent doses are necessary to diminish the spasm of deglutition. Remedies which paralyze muscles have been advised, especially curare. A case recovering from this treatment, but which was most probably lyssophobia, prior to the time of preventive inoculation, gave me the idea of treating the disease with curare. By very large doses, nearly $\frac{1}{2}$ grain in ten hours, one-fifth of the lethal dose calculated according to animal experiments, decidedly diminishes the attacks in the beginning of the affection, finally, however, in controlling delirium, chloral and curare were without effects. Then continuous chloroform narcosis, even if its application is difficult appears to me to be the most humane method. With sufficient attention we may succeed in keeping the unfortunate patient in this condition until death occurs.

This description cannot be closed without bringing up the practical and important question and answering it: *What is to be done in general in case of a dog bite?*

Every wound, from the bite of a dog, even although nothing is known regarding rabies in the dog, is to be looked upon as serious—other wound infections may also occur—and should be cleansed at once by allowing them to bleed and by disinfectant washes. Under all circumstances the attempt should be made to watch the dog in the days following the bite. If the dog remains in a normal condition for eight days afterward there need be no fear.

If, however, cases of rabies are present in the region or if this district is near to one in which cases are known, every dog bite as well as any other bite of a quadruped even if no symptoms are noted in the animal is to be looked upon as very suspicious, the wound is to be cauterized at once with an improvised cautery and then disinfected. The animal, if possible, is not to be killed but to be carefully guarded and observed by a veterinarian. If the animal becomes sick at all, and still more if it shows symptoms of rabies, an Institution in which protective inoculation is practised is to receive the patient that has been bitten at once. In Berlin the treatment is free and may be applied in such a manner that the patient is permitted to go home.

By observing these precautions it will be possible in most cases to prevent the development of this terrible affection by protective inoculation.

ANTHRAX

By A. NICOLAIER, BERLIN

ANTHRAX is an acute infectious disease due to the bacillus of anthrax. The disease occurs principally in animals, especially in the herbivora, but it also has interest for the practising physician as occasionally it is transmitted by animals either directly or indirectly to human beings, developing in man with a similar clinical picture and according to the point at which infection takes place, may show various constitutional peculiarities. We must, therefore, place anthrax in that group of infectious diseases which are transmitted from animal to man, which run their course with the same, or similar symptoms in animal as in man, this group of infectious diseases for this reason being designated as zoonoses.

Even in ancient times anthrax was known as a pestilence of animals, and, on account of the great numbers that perished from it, it was particularly feared. Although from the epidemic appearance of the affection in animals the infectious nature of anthrax could be concluded, it was only determined with certainty in the second decade of the last century by experimental transmission from animal to animal, and then about the middle of the last century, a vegetable parasite, the bacillus of anthrax, was discovered as the cause of the disease. Pollender deserves the credit, in 1849, of having first recognized the anthrax bacillus in the blood of animals affected by the disease, and in his description in the year 1855 he correctly designated these structures as of vegetable origin; however, Davaine, in the year 1863 was the first to show the causative relation of these bacilli to anthrax, which then in the seventh and eighth decades of the previous century were proved by the important investigations of Robert Koch regarding the anthrax bacillus.

In man infection by the toxin of anthrax and the principal cutaneous changes due to it, were first described by Fournier in the year 1769.

I shall first call attention to the important *morphologic* properties and to the *biology* of the bacillus of anthrax, in so far as this knowledge is necessary for the appreciation of the *etiology* and the *pathology* of the disease.

The anthrax bacillus presents a large slender immotile rod with rounded ends, its breadth being about 1–1.5 μ , the length varying between 3 and 10 μ and more. Not only in culture, but also in the animal organism, the bacilli grow in threads and those observed in the blood or in animal organs show in stained preparations an appearance as of being composed of individual bacilli, club-shaped at their ends. Staining succeeds readily with basic anilin dyes, they also stain according to Gram.

The anthrax bacillus is not very choice in regard to its culture media. In the presence of a plentiful supply of oxygen, and in temperatures of from

15° C. to 45° C. it develops very well even upon turnips, upon the excrement of cows and even in contaminated earth. If the anthrax bacillus is cultivated upon plates with nutritive gelatin, in the course of a few days, at the temperature of the air, it forms round grayish white colonies, the gelatin becoming liquefied in the surrounding area, showing microscopically a light centre surrounded by a light grayish or brown mass which consists of flocculent strands. In stab cultures upon gelatin they form along the course of the inoculation a whitish strand-like proliferation from which fine threads radiate at right angles into the culture media and after from two to three days here also a slowly progressing liquefaction of the culture media occurs. If the anthrax bacilli are cultivated at a somewhat higher temperature at about 30° C. upon agar, where it grows as a white, thick thready layer, or upon blood serum which also becomes liquefied by the growth in a short time, the formation of oval spores then occurs which are about twice as long as they are wide, and which become free after the threads have dissolved. Conditions for spore formation are temperatures of from 18° C. to 40° C. and, above all, a plentiful supply of oxygen, and for this reason spore formation does not occur in the tissues of the living animal nor in the undamaged cadaver. The spores, in contrast to the bacilli, are extraordinarily resistant to external influences, such as heat, drying and disinfecting agents. Even though, according to the provenience of the spores in this respect, certain variations exist, this much is certain that the spores of the anthrax bacilli, even though kept for many years at the usual temperature, in the dark and dried, retain their full virulence, that decomposition may act upon them for months without damaging them, and that a 5 per cent. carbolic acid solution only after many days, in very resisting varieties of spores even after forty days, and a volume of steam acting for ten minutes will render them harmless.

Regarding the manner of distribution of anthrax, it is of the greatest importance that the anthrax bacillus, as already mentioned, shows but slight selection in regard to its culture media; for this reason it occasionally develops saphrophytically and that, further, its spores are so extraordinarily resistant. Anthrax bacilli which find their way into the ground in the discharges of affected animals or in burying the anthrax cadaver may, under favorable circumstances, develop and form spores, which infect plants growing in the earth. The conditions for their saphrophytic growth is found by the bacillus in certain regions, especially in the neighborhood of swamps and rivers, in which, besides sufficient moisture, favorable temperatures and plentiful amounts of decaying vegetable matter are present. From these regions the spores of the anthrax bacilli are carried occasionally by inundations to grazing places where they may remain for a long time or may even undergo further development.

This makes it plain why in certain regions especially near rivers, anthrax occurs so frequently in animals and in some years, especially in summer, shows an epidemic distribution. These regions, for this reason, have been designated *anthrax districts*.

On the other hand, this explains why the disease so frequently occurs in herbivorous animals especially in cattle and sheep, whereas omnivorous or carnivorous animals are comparatively rarely attacked. Even though occa-

sionally a herbivorous animal is infected by the stings of an insect that has taken up the anthrax poison from a sick animal or from its cadaver, this is quite exceptional. In the greatest majority of cases in which spontaneous development occurs, the infection has unquestionably taken place by taking up the spores of the anthrax bacilli with the food. Occasionally wounds of the oral and pharyngeal mucous membrane, which may even be produced by food infected with the virus bring about the disease; as a rule, however, the animals are made sick as a result of the taking up of anthrax spores which adhere to their bodies thus reaching the gastro-intestinal canal. It has even been experimentally proved that in cattle, sheep and also in goats and horses provided small amounts of spores are for a long time administered with the fodder, intestinal anthrax develops comparatively readily.

In *animals*, anthrax does not always show the same clinical picture. In rare cases, in which the infection arises from wounds of the skin or of the mucous membrane, at the point of entrance of the virus, local phenomena first appear which are characteristic of anthrax; the anthrax carbuncle or anthrax edema, which are then mostly followed by general symptoms.

The affection which develops by way of the gastro-intestinal canal may terminate fatally in half an hour in sheep, showing the symptoms of cerebral apoplexy; in cattle and sheep, in the acute cases, the affection lasts from several hours up to a day, in the subacute cases perhaps from two to seven days, the most prominent symptoms being restlessness, difficulty in respiration, cyanosis, loss of appetite, colic, diarrhea, high fever, hemorrhagic urine, loss of flesh, increasing debility, the appearance upon the skin occasionally of secondary anthrax carbuncles and anthrax edema.

At the autopsies of animals there is found in general enlargement of the spleen, parenchymatous changes in the liver, kidneys, and heart, hemorrhages in different organs, collections of fluid in the cavities of the body, hemorrhagic infiltration of the mucous membranes, especially those of the gastro-intestinal tract, lymph-gland enlargement and a tarry consistence of the blood, in which, as well as in the different organs, anthrax bacilli can be demonstrated.

In smaller animals also, such as mice, guinea-pigs and rabbits, that are often infected with the exciting cause of anthrax for diagnostic purposes, and which perish in from one to three days after having shown very characteristic symptoms, the autopsy findings are usually those of an enlargement of the spleen, besides parenchymatous changes in the liver, the kidneys, and the heart, besides more or less extensive edema at the point of inoculation, where, as a rule, but few anthrax bacilli are found; in the blood and in the capillaries of the internal organs the bacilli are present in much greater numbers.

I have briefly described the symptomatology and the pathologic anatomy of anthrax in animals because the practical physician must have some knowledge of them. The source of infection for man, as I have already indicated, is exclusively the animal infected by anthrax. As a result of this, especially those persons whose occupations bring them in contact with sick animals or with their cadavers, such as cattle dealers, shepherds, butchers, skin-dealers, etc., or those who handle the products of infected animals or use them in manufacture such as furriers, tanners, brush-makers, etc., are subject to the disease. As the male sex shows the largest contingent in these occupations,

they are more liable to attacks than women and children. Further, the transmission of anthrax from animal to man is explained by the observation, that during periods and in districts in which the affection appears in animals in the form of an epizootic, thus especially in anthrax districts during the summer, a larger number of cases of anthrax occurs in human beings.

Fortunately man is much less susceptible to infection with the poison of anthrax than are herbivorous animals. And for this reason even during the time of an epizootic, in anthrax districts, the number of cases in animals and in man are in great disproportion. Human beings, after recovery from anthrax infection, show no immunity, but may acquire a new affection after a relatively brief period.

The pathogenic agent of anthrax may enter the human organism in various ways. Unquestionably the skin is the most frequent port of entrance. Bollinger even maintained that the pathogenic agents might find their way through the intact skin by way of the follicles and thus enter the human body. If this is correct, which is doubted, however, by Babault and Prosperi, it can only be true in rare exceptional cases. As a rule, the requirement for infection with the virus of anthrax on the part of the skin—and the same is true also for the mucous membrane, from which, however, the affection much more rarely takes its point of origin—depends upon a rupture of continuity. In such wounds, the anthrax bacilli enter by means of the blood or of blood-containing secretions and this occurs most frequently in veterinarians who treat sick animals, or in shepherds or hostlers who attend to animals affected by anthrax; much more frequently, however, the affection occurs in persons who slaughter sick animals or that skin them after death, therefore especially in butchers and the like. Naturally, it is not so very rare in them that the bacilli are only transmitted by means of an injury to the skin, which has occurred in their occupation. Occasionally the affection may occur from the sting of flies that have come in contact with animals affected by anthrax or of the cadavers or from the bite of animals that have eaten meat contaminated with anthrax.

Infection by means of the skin may occur further, particularly in persons who come in contact with the products of anthrax-infected animals such as skins, hair, wool, etc., or in rags that are worked up in anthrax districts, for especially in these substances, particularly those coming from Russia, especially in skins and hair coming from Russia and India, the resistant spores of the anthrax bacilli are frequently found in large numbers; those handling these products having lesions of their skin or mucous membrane permit the germs to enter and thus to develop further. In this connection, especially dealers in skins, tanners, furriers, harness makers, and workmen engaged in spinning horse hair, brush makers, are particularly endangered, and the danger of contagion is all the greater as the infection from these substances which they are required to handle may also occur in other ways than by wounds of the skin or of the mucous membrane. These products for the most part are handled in a dry condition, the spores of the anthrax bacilli are but slightly adherent and are readily shaken off with the dust, are then inspired with the respiratory air into the lungs of the workmen, in whom then the so-called *pulmonary anthrax* develops. This disease has been known for a long time.

About 1830 among wool-workers in England a disease was observed running its course with very characteristic symptoms to which the name *wool-sorters' disease* was given; the true nature of the affection at that time was not suspected, and only in the year 1881 Spear and Greenfield simultaneously were the first to show, and this was confirmed upon many occasions later on, that wool-sorters' disease was due to the bacillus of anthrax, and that the affection was conveyed by these parasites finding their way into the lungs of human beings. At this time we must look upon the affection which occurs in rag sorters in paper factories, as the result of the entrance of anthrax spores into the lungs, which has also been observed in Austria, especially from the conclusive and accurate investigations of Eppinger, showing itself in a similar manner to wool-sorters' disease, *rag-pickers' disease* ("Haderkrankheit"), the etiology of which was also unknown for a long time.

I wish to add that Buchner succeeded in producing anthrax in guinea-pigs and mice by the inhalation of anthrax bacilli spores which were mixed with powdered coal and talcum.

There is still a third mode of infection, although much rarer, which occurs in workmen that handle the skins, hairs, etc., of animals affected by anthrax. The spores of the bacilli which remain upon the substances which are used by them, may also either directly come in contact with food, or indirectly by contamination of food substances, reach the oral cavity of the workmen and thus enter the intestinal canal where they give rise to *intestinal anthrax*.

As has been determined, in experiments upon animals, the spores of anthrax are not damaged by the gastric juice for, as I have already mentioned, cattle, sheep and other animals which for a long time have been fed with small quantities of spores are later attacked by intestinal anthrax and even natural anthrax develops in herbivora, as is well known, especially by the intake of anthrax spores into the gastro-intestinal tract with the fodder. In man intestinal anthrax is much less common than in animals because man has less opportunity of taking up the virus with his food; apart from the transmission of the anthrax spores to the gastro-intestinal tract, which occurs occasionally in workmen, infection takes place in man only by partaking of the milk of animals suffering from anthrax, or from the products produced from it such as cheese and butter, and especially from eating meat from an anthrax animal. Especially after the use of infected meat, several anthrax epidemics have occurred in the human subject. These epidemics have led to the interesting observation that meat, contaminated with anthrax, does not always cause a resulting infection, for persons, in whom it has been proved, that they have partaken of meat obtained from an animal which had suffered from anthrax, the meat having been eaten in quite large amounts without having been sufficiently boiled or fried, did not acquire the disease. This may probably be explained in the manner, that anthrax bacilli which are especially liable to cause infection, spore formation not taking place in the body, are destroyed by the gastric juice; a fact that has been determined in animals, and thus the affection has not developed. In spite of this the use of contaminated meat, even when boiled or fried, must be prohibited under all circumstances. Apart from the fact that in the acts of mastication and deglutition, anthrax bacilli may find their way into small wounds of the mucous membrane of the

mouth, pharynx and esophagus, and with an altered stage of digestion reach the intestine in a virulent condition, a greater danger consists in the presence of spores in the meat, for the spores, as is well known, may readily form upon the surface of the meat, if the meat is preserved at a somewhat higher temperature; conditions favorable for spore formation. Infection of the intestinal canal will always succeed the use of this kind of meat, as the spores are able to pass the stomach in an undamaged condition.

In rare cases of anthrax the point of infection cannot be determined nor does the autopsy clear the situation. Perhaps in these cases the pathogenic agent has entered by means of the lungs or by the gastro-intestinal canal, not having produced, as is so usual, the characteristic changes at the point of infection.

It must be noted that occasionally *transmission of anthrax has been observed from man to man*. This is, however, very rare. It may occur directly, as in the case of undertakers, or persons may transmit them who have infected fingers, or it may take place by means of instruments that have been used on persons affected by anthrax and which have not been sufficiently disinfected. In the last mentioned manner, according to an observation of Jacoby, 4 persons were affected by a Pravaz syringe which had been used for subcutaneous injection in a person affected by anthrax.

SYMPTOMS

The *clinical picture* in man varies greatly; the course of the affection is particularly determined by the point of invasion of the pathogenic agent.

If the poison enters by way of the skin, as is the most frequent mode, after a *period of incubation* of about from two to three days (only rarely is this longer than fourteen days) the local phenomena develop at the point of infection which, in the greatest majority of cases show themselves in the form of a primary anthrax carbuncle (*carbunculus contagiosus* or *pustula maligna*). At first, accompanied by sensations of itching, a small red point forms, often with a black centre, which soon becomes a papule. In this papule there occurs, as a rule, about fifteen hours after the onset of the eruption, often with the addition of sensations of burning, the so-called *anthrax vesicle*; a vesicle filled with a yellowish, or reddish contents, usually about the size of a pea, which for the most part ruptures, the surface then forming an eschar. From the second day on the papule, and with it the eschar, grow (also invading the deeper tissues), finally the eruption may attain the size of a walnut, producing but slight or even no pain at all. The older the eruption, the harder the eschar becomes, and the more does the middle portion sink. Often the eruption is demarcated from the surrounding skin by a somewhat elevated red or bluish-red areola, which frequently contains an individual vesicle or groups of the same; for the most part the surrounding areas often to a wide extent show but slightly painful, hard inflammatory swelling, and in this area inflamed lymph vessels may be noted, being visible as red striæ or bands. As a rule, the carbuncle requires a period of from five to eight days to develop in this manner. In some cases a painful swelling of the neighboring lymph glands appears to be the only accompanying

phenomena, on the other hand there may be a well-defined constitutional disturbance, especially lassitude, dizziness, loss of appetite, and not rarely is there a moderate rise in temperature. Occasionally, a few days after the carbuncle has appeared gangrenous processes develop in its surroundings which are then followed by a severe, for the most part fatal, general infection. Fortunately, the carbuncle frequently heals, with suitable treatment, sometimes even without this, in the manner that the infiltration in its neighborhood and the enlargement of the lymph glands gradually disappears. The eschar is desquamated after some time and now healing occurs under the production of a larger or smaller cicatrix. The carbuncle of anthrax shows a preference for the soft and thin cutaneous parts that are not covered by clothing, such as the neck, the face, and the upper extremity, and here especially on the hands.

In rare cases after an infection of the skin with the toxin of anthrax instead of the carbuncle, *anthrax edema* develops. Its point of selection is either the upper or lower eye-lid showing itself in the form of a doughy, edematous, pale swelling which later on becomes red and hard, and upon which frequently discolored vesicles with hemorrhagic contents or dark eschars form. If the latter have developed, then the eruption shows great similarity to the anthrax carbuncle. The edema frequently develops over the other parts of the face and may even invade the mucous membranes of the mouth, pharynx and tongue.

The edema develops less frequently upon the upper extremity and upon the throat, but it is almost always accompanied by inflammation of the neighboring lymph glands and frequently by an inflammation of the lymph vessels; not rarely is there added to this edema, even after it has been developed for two to three days, a fatal general infection.

At this point I should like to quote the case of an undertaker affected by cutaneous anthrax reported by Fränkel and Orth; in this patient at the point of invasion of the virus only a lymphangitis developed; so far as I know no second case of this kind is noted in literature.

In an infection of the mucous membrane, which is comparatively rare, occurring most frequently from the conjunctival and nasal mucous membrane, in rare cases also from the tongue and the tonsils, the changes resembling carbuncle are also noted; they are painful, enlarge gradually, for necroses and infiltration of the surrounding areas in which decided inflammation occurs as well as enlargement of the regional lymph glands are noted.

As has already been mentioned, the carbuncle as well as the edema of the skin and mucous membranes may be followed by a general infection, and this a short time after its development, in the manner that the bacilli are distributed all over the body from the point of invasion. The symptoms which then appear vary greatly in individual cases, according as the different organs are implicated in the affection.

Only in the rarest cases are constitutional symptoms absent, such as pains in the head, in the limbs and in the joints, further, decided lassitude; the pulse frequency is regularly more or less increased and there is usually decided fever which later on becomes continuous or which may run a remittent course.

I shall call attention to the symptoms on the part of the abdominal and

chest organs, which occasionally become prominent, in the description of intestinal and pulmonary anthrax, and will only add that cerebral symptoms, such as mental dulness, somnolence, delirium and spasm are rare in cutaneous anthrax and are usually only observed if the local phenomena are present in the face and upon the neck.

The patient succumbs to the general infection in from seven to ten days, in individual cases the fatal outcome may occur later, being due to a septicopyemia, as in some cases suppuration occurs in the carbuncle.

In **intestinal anthrax**, **mycosis intestinalis**, the first symptoms are those of the appearance of lassitude, pains in the head and limbs, occasionally also in the lower abdominal region, further vertigo and chills, to which there are soon added symptoms on the part of the gastro-intestinal canal: coated tongue, anorexia, eructation, nausea, vomiting occasionally of bilious or even hemorrhagic masses, increased thirst, pain in the abdomen, often accompanied with meteorism and pain upon pressure. Occasionally a collection of fluid may be noted in the abdominal cavity, with enlargements of the spleen and liver. In the most cases profuse diarrhea is present, the stools being admixed with blood. Hemorrhages from the mouth and nose are also occasionally present. As a rule, the pulse frequency is increased as is also the respiration, which appears to be labored; often there is more or less well developed cyanosis. Pulmonary phenomena such as catarrh and signs of infiltration are noted now and then, more frequently there are nervous disturbances, restlessness, delirium, coma and spasms. Upon the skin small (secondary) carbuncles may be present, hemorrhagic vesicles, gangrenous and phlegmonous changes and hemorrhages are not even rare upon the mucous membranes. The temperature is increased during the entire course of the affection, and falls before the lethal termination, which may occur in thirty-six to forty-eight hours from the onset of the disease, but which, as a rule, lasts from five to eight days.

The symptoms of **pulmonary anthrax**: In from two to four days after the virus of anthrax has gained access to the lungs, prodromal symptoms occur in rare cases, such as nausea, lassitude, vertigo, headache, coryza and cough; for the most part, the affection begins suddenly with these symptoms, often with a chill followed by high temperature. The patients are very weak, have a sense of constriction in the chest, complain of stitches in the side, and with this there is dyspnea and more or less decided cyanosis. An early symptom is a high graded cardiac asthenia; the cardiac sounds are soft, the pulse is small and increased, often arrhythmic. Cough is always present and soon a muco-purulent, often hemorrhagic sputum is expectorated, which is sometimes even rusty and prune-juice like and in which for the most part anthrax bacilli may be demonstrated.

In the lungs, in the first days of the disease, only the signs of catarrh can be noted, later the signs of consolidation of the pulmonary tissue are found: dulness, ringing râles, feeble and bronchial respiration, and often the signs of a dry or exudative pleurisy may be observed in the patient. Enlargement of the spleen is frequent, jaundice has been noted in but a few cases. The urine may contain albumin, now and then also blood and sugar. In the course of the affection the temperature gradually falls. The sensorium for the

greater part of the affection remains free, only shortly before death does the mind become cloudy, and in this period delirium occurs. Cerebral symptoms, as well as symptoms on the part of the gastro-intestinal tract which were mentioned as occurring in intestinal anthrax, only occur when the brain or the intestinal canal develops changes due to the influence of the bacilli. In most cases of pulmonary anthrax death occurs with the symptoms of an increasing cardiac asthenia and collapse between the third and the sixth days of the disease, or even sooner.

Finally, I must briefly mention two cases of anthrax which showed an abnormal course. In the one case, reported by Curschmann, principally cerebral phenomena were prominent and the autopsy revealed a hemorrhagic encephalitis, whereas the second case, described by Baumgarten, ran a course resembling an ascending paralysis.

Whether anthrax in man may run a course resembling septicemia, as is the case in inoculation anthrax in animals, is still an open question.

PATHOLOGY

The pathologico-anatomic changes which are noted at the autopsy in many respects are quite characteristic. The phenomena upon the skin, the anthrax edema, the anthrax carbuncle, the edematous and phlegmonous surrounding areas, occasionally showing vesicles, hemorrhages and gangrenous infiltration, I have already described. I will only add here that the carbuncle upon section at first shows a yellowish-red and later brownish-red to brown-black infiltration, that an eschar is present in the central parts which often continues into the edematous hemorrhagic infiltrated subcutaneous connective tissue. Upon microscopic examination of the anthrax carbuncle, anthrax bacilli are found, especially in the deeper areas and in large amounts in the lymph vessels of the tissues surrounding the eschar which also contains plentiful quantities of leukocytes besides smaller numbers of erythrocytes. In the escoriated areas of the carbuncle but few bacilli are present, other microorganisms, especially pyogenic ones which secondarily have developed in the necrotic tissues, are found in greater numbers, particularly if the carbuncle is less recent.

Carbuncles as well as anthrax edema are found side by side with hemorrhages and inflammatory changes of the mucous membrane of the mouth and pharynx, but they are very rare. More frequently these phenomena are found upon the mucous membrane of the gastro-intestinal tract, especially the appearance of carbuncles. Whereas they occur individually in the stomach and in the lower portion of the bowel, and here even more rarely, they are found more frequently and in greater numbers in the small intestine especially in the jejunum and the upper portion of the ileum, being usually found upon the wall opposite to the mesenteric attachment. They appear here as more or less elevated infiltrations, sometimes attaining the size of a cherry, having a soft consistence and being of a reddish color. If necrosis has already formed, they then show a dark gray color. Now and then even ulceration may be noted in them. In the carbuncles of the mucous membrane, especially those of the intestine, anthrax bacilli can be demonstrated particularly in the deeper layers, whereas they are less in number in the necrosed and ulcerated areas,

being displaced by other microorganisms. Often hemorrhages and inflammatory changes of the peritoneum, the latter often giving rise to effusion which may also contain blood, are noted, and this is not necessarily in keeping with the seat of the carbuncle. As the regional lymph glands in disease of other mucous membranes and the skin, so are the mesenteric and retroperitoneal lymph glands also enlarged, as a rule, more or less hemorrhagically infiltrated, when they show a grayish-red to dark red color.

The liver is but rarely enlarged, and apart from hemorrhage shows no abnormal condition. On the other hand the spleen, although not always, is larger and darker than normal and of softer consistence. The kidneys are unaltered, as a rule, except that hemorrhage may occur, still upon microscopic examination parenchymatous and interstitial processes may sometimes be recognized.

The thoracic organs in pulmonary anthrax are especially changed and this to a decided extent. The lungs show hyperemic areas, sometimes hemorrhagic infarct, as a rule, pneumonic areas of varying size but only in rare cases does gangrene occur. Inflammatory changes of the pleura, with and without effusion and hemorrhagic enlargement of the bronchial glands are regular findings; the tracheal and bronchial mucous membranes as well as the mucous membranes of the larynx frequently show besides hyperemia and hemorrhages, cellular infiltration. In the heart subendocardial hemorrhages, parenchymatous and fatty degeneration are often present. Eppinger occasionally found changes in the valves of the endocardium in which anthrax bacilli could be demonstrated.

In the brain, besides slight hemorrhages which are not rare even in the meninges, small foci of softening occur. The blood, which often shows a marked increase of leukocytes, also reveals anthrax bacilli as well as the capillaries of the principal organs, in the exudate of the serous cavities and in the sputum in disease of the lungs.

PROGNOSIS

Regarding *prognosis* in anthrax, the localization and extent of the disease is decisive.

In anthrax of the skin the prognosis is by no means unfavorable for I have already mentioned that *malignant pustule* not only heals under favorable treatment but also sometimes spontaneously. According to the statistics of W. Koch including 1,473 cases of cutaneous anthrax, recovery occurred in 68 per cent. of the cases. Recovery must naturally be excluded if in connection with the local phenomena a general infection develops and this appears to be frequently the case, if the anthrax eruptions are found upon the head, upon the neck and upon the tongue besides edema being present. As a result of this, under these circumstances, the chances in cutaneous anthrax are somewhat less favorable.

A bad prognosis is given by intestinal and pulmonary anthrax. Occasionally, as the observations of epidemics teach, cases of intestinal anthrax run a mild course and then recovery occurs, and also in pulmonary anthrax cases occur in which the phenomena on the part of the lungs and pleura are

not well developed, the cardiac asthenia and temperature not reaching high grades and in consequence in the course of two or three weeks running a favorable course; in general this is rare, for the most part the patient succumbs to the disease. In pulmonary anthrax the mortality amounts to 87.1 per cent.

DIAGNOSIS

The diagnosis of anthrax is easy if the symptoms of cutaneous anthrax, carbuncle or edema are present, and it can be learned from the patient that he has had an opportunity in the course of his occupation to infect himself with the virus of anthrax. If this history cannot be obtained the diagnosis may be difficult, because we are acquainted with cutaneous affections which show a certain similarity to the eruption of anthrax; thus, the carbuncle in its first stages may resemble the nodule of glanders, when it is more developed it may resemble benign carbuncle, further the carbuncle of plague; anthrax edema may resemble erysipelas and phlegmonous changes in the skin. In the differential diagnosis the differences of these various affections from anthrax of the skin and the other accompanying phenomena must be considered; thus, the slow and painful development of benign carbuncle, the marked inflammation of its surroundings, the necrotic masses and the pus flowing from numerous openings, further, in glanders the numerous variable eruptions upon the skin, the often simultaneous affection of the nasal mucous membrane, in erysipelas the sharp demarcation from the unaltered skin, the transition of phlegmons into a stage of suppuration, in anthrax only the presence of a pathogenic agent in the secretion of the carbuncle or in the fluid of the edema can make the diagnosis certain.

The diagnosis of *primary intestinal anthrax* should be considered when the characteristic changes and the history point to an infection from the use of meat from animals affected with anthrax, or from the taking up of anthrax spores by way of the mouth. From the clinical symptoms alone the disease can only be diagnosticated in its later stages, when secondary anthrax carbuncles develop upon the skin besides the other phenomena.

Primary pulmonary anthrax can be recognized with difficulty from the clinical picture, for in many respects it resembles fibrinous pneumonia and especially when it is complicated by symptoms on the part of the gastrointestinal tract and the brain. For this reason it is of especial importance to ascertain whether the patient has had an opportunity of inhaling spores of anthrax bacilli.

In the diagnosis of intestinal as well as pulmonary anthrax, the positive result of the demonstration of anthrax bacilli is decisive. Naturally, we must not limit ourselves in the bacteriological examination of cutaneous anthrax only to the microscopic demonstration of bacilli, but the pathogenic agent must be identified by culture, or, even better, by inoculation into mice and guinea-pigs. Besides, the proof by puncture or by inoculation of animals also occurs in cases in which the bacilli cannot be demonstrated microscopically.

PROPHYLAXIS AND THERAPY OF ANTHRAX

It has already been mentioned that anthrax almost exclusively is conveyed from animal to man and for this reason the limitation of the number of affections in animals is of the greatest importance for the prophylaxis of human anthrax. In this respect we may hope for success from the protective inoculation of animals against anthrax infection which was experimentally tested by Pasteur and then also tried in practice. Protection by inoculation is attained in animals in that they are infected with anthrax cultures which are grown at a temperature of 42° C. to 43° C. and attenuated. Naturally, some failures have been observed and a number of animals have perished from the inoculation; in spite of this, the method is to be advised, for the diminution in the mortality of anthrax under its influence is a very decided one. In France for the years 1892 to 1893 the mortality under protective inoculation in cattle diminished from 5 per cent. to 0.34 per cent., in sheep from 10 per cent. to 0.94 per cent.

In this manner the great danger can be decidedly diminished which threatens persons who are compelled to come in contact with skins and hair of animals, or with rags that are brought from anthrax districts. As protective inoculation has not been introduced in many anthrax districts, and on the other hand a thorough disinfection of skins without damaging them is impossible up to now, and as disinfection of rags cannot be readily accomplished, the best protection for workmen against anthrax infection would be the prohibition of the introduction of these products from anthrax districts. So long as this is not done, workmen in factories, in which these products are utilized where possibly spores of anthrax bacilli may adhere, must be protected in every direction against the taking up of the virus of anthrax. This can only be attained by the removal of the dust which adheres to the hair, rags, etc., by means of machines and its destruction by fire. By a thorough ventilation of the factories and by disinfection of the walls and floors, protecting the workmen by proper respirators, by a change and disinfection of clothing and cleansing the hands of the workmen by a 1 to 1,000 corrosive sublimate solution after the work is done, this may be accomplished. By the prohibition of bringing food into the work-rooms and eating it there, and by the protection of wounds by suitable bandages, the same ends are reached.

The laws promulgated in Germany, June 23, 1881, and May 1, 1894, looking to the suppression of animal diseases, and a publication of this report on June 27, 1895, has done much in the prophylaxis of anthrax in man. According to this law the owners of animals affected with anthrax or animals that are suspected of having anthrax, are made acquainted with the infectiousness of the disease and its contagiousness. Sick animals are not to be slaughtered, their flesh and milk are not to be used, and their skin and hair are not to be sold. Operations upon animals attacked by anthrax and autopsies are only to be done by veterinarians, and persons having cutaneous wounds are not allowed to come in contact with sick animals nor with their cadavers. The cadaver is not to be skinned and must be cremated, or, by prolonged boiling or by other chemical means must be disinfected and rendered harmless and buried at least 3 feet deep. All substances that have come in contact

with the blood, secretions and excretions of sick animals, must be disinfected in the proper manner and naturally when the disease occurs in man the same protective measures must be used.

If persons injure themselves in their occupation about sick animals, the wound is to be cauterized early, disinfected and protected by a bandage.

Notification of anthrax in man is necessary in almost all parts of Prussia and in other German States with the exception of Saxony, Würtemberg, Baden, Alsace-Lorraine, and a number of the smaller States.

The **therapy** of anthrax, in an existing cutaneous eruption, must be directed to prevent a general infection, and this can be best attained if the toxin in this eruption is rendered harmless. Naturally, a result can only be attained if this treatment is begun as early as possible, and that in the first two days after the first appearance of the symptoms. Small carbuncles, especially also the regional lymph glands, should be excised and the wound cauterized with a thermo-cautery. If the carbuncles are larger, caustics may be employed for this purpose, such as fluid carbolic acid, fuming nitric acid, caustic potash, corrosive sublimate, eventually after a previous incision; still better for this purpose is a thermo-cautery. These measures may be combined with a subcutaneous injection of bactericidal fluids in and around the affected cutaneous areas. For this purpose a 2 per cent. to 3 per cent. solution of carbolic acid, or tincture of iodine can be used mixed with a like quantity of water which may be injected several times daily. In employing any of these measures it is advisable to keep the affected part quiet and to suspend it if possible.

It will be frequently noted that with this treatment cutaneous anthrax will remain local. Naturally, the same result may be observed if an expectant treatment of cutaneous anthrax is followed according to the process of Kurt Müller, the affected limb properly bandaged and suspended, the eruption covered with gray salve, the patient well nourished and large doses of alcohol administered.

After *general infection* has occurred and in the case of *intestinal* and *pulmonary anthrax*, besides proper nutrition and the administration of proper amounts of alcohol, a symptomatic treatment must be employed. A trial may be made with the internal administration of quinine (4 grams divided into 4 doses) or quinine (0.2 to 0.5 grams per dose) combined with carbolic acid in doses of 0.1 as often as 10 times daily (Leube). Further, preparations of iodine (iodine 1.0, potassium iodide 2.0 in 3 litres of water, of this 1 litre per day as a drink [Garré]). In gastro-intestinal anthrax, calomel (0.1 to 0.2 several times daily). In pulmonary anthrax the inhalation of a disinfecting solution (1 per cent. to a 2 per cent. carbolic acid solution) is indicated.

GLANDERS, FARCY

By A. NICOLAIER, BERLIN

GLANDERS or farcy (*Malleus humidus et farciminus*, *Maliasmus*) is an *infectious disease* due to the *bacillus of glanders* (*bacillus mellei*), which occurs particularly in the horse, more rarely in the ass, and in the mule, and which may run an acute as well as a chronic course. As glanders may occasionally be transmitted from these animals to man and then show a similar clinical picture, this affection as well as anthrax is classed with the *zoonoses*.

In spite of the fact that the transmissibility of glanders from animal to animal has been known since the fifth century, the knowledge that the human being may be infected from the animal was due to Osiander, in the year 1783, and only in 1821 was the clinical picture of human glanders accurately described by the Prussian military physician, Schilling. The successful transmission of glanders from man to the horse and to the mule, which Travers and Coleman in 1826, and then Elliotson in 1833, succeeded in accomplishing, showed that the disease in man was due to the same cause as in animals, and this proof was definitely settled in the year 1882 when Löffler and Schütz discovered the bacillus of glanders as the actual cause of the affection in animals, and Weichselbaum, in 1885, demonstrated that this bacillus was also the cause of human glanders.

We shall first describe the *important properties of this pathogenic agent*.

BACTERIOLOGY

The bacilli of glanders represent small, slender, immotile rods rounded at their ends, resembling tubercle bacilli, and having a length of 1.5 to 5 μ , and a thickness of 0.25 to 0.4 μ . Occasionally clubby swellings are noted, the bacilli sometimes being somewhat bent and forming in cultures, as I have lately observed, branching and intertwining threads, as are also noted in the streptothrix, so that possibly the bacilli of glanders may be regarded as belonging to this group of microorganisms. The bacillus of glanders does not stain according to Gram. The recognition of the stained sections of tissue is difficult, as the pathologic tissue takes up and retains the color better than the bacilli themselves. For this purpose I should advise preparing the sections according to Kühne, treating them for six to eight hours with a methylene-blue solution containing carbolic acid, and decolorizing them with water containing acetic acid, or, according to the method of L. Aschoff, of staining the sections with Unna's plasma-cell stain (staining with polychromethylene-blue and subsequent differentiation with a glycerin-ether mixture). In cover-glass preparations the staining of bacilli is much easier. It is only necessary

to allow the preparation to remain sufficiently long in Löffler's alcoholic-alkaline-methylene-blue solution or in a hot carbo-fuchsin solution. Frequently in preparations stained in this manner bacilli will be found in which dark and light areas alternate; these lighter zones have been looked upon as spores; but whether this view is correct is certainly questionable. Until now it has been an open question whether glanders bacilli form spores at all.

The bacillus of glanders is comparatively resistant to certain external influences; thus, decomposition is only capable of rendering them inanimate after twenty-four days, also they appear to be less sensitive to drying. Spores when spread in a thin layer, remain virulent for weeks, and Löffler found them capable of life in dried cultures even after three to four weeks. The resistance of the glanders bacilli to drying does not appear to always be the same, for there are some observations of Bonome, according to which the bacilli lose their virulence after drying for ten days, and it is known that if the pus from horses affected by glanders is dried for fifteen days it no longer proves to be infectious. In a moist condition the bacilli are said to retain their virulent properties for thirty days. They are but very slightly resistant to high temperatures, and to a 1 per cent. solution of corrosive sublimate; at the temperature of boiling water the bacilli are killed in from two to three minutes, whereas a 1 per cent. solution of corrosive sublimate renders them inactive in fifteen minutes. For this reason the employment of high temperatures and a 1 per cent. corrosive sublimate solution is advised, above all, in the disinfection of the secretions of animals and human beings affected by glanders, and also for other infected substances.

At temperatures of from 25° C. to 45° C. the bacilli may be cultivated upon the usual bacteriologic media; they grow best at a temperature of 37° C. upon glycerin agar upon which they form whitish, transparent, smooth-bordered granular colonies; along the course of inoculation they form moist, glistening coatings. I desire to call special attention to the growth of the bacilli upon potatoes; it is so typical that it may be utilized in the diagnosis of glanders bacilli. Upon this medium, best at a temperature of 37° C., after about two days a thin yellowish deposit is formed, which after about eight days takes on a brownish-red color surrounded by a bluish margin.

During its growth in cultures, the bacillus develops products of metabolism, of which two have been somewhat more closely studied. One of the products is *mallein*, a protein which was produced almost simultaneously by Kalning and Preusse from cultures of glanders bacilli by extraction with water, or with watery glycerin. This substance is of especial interest because it is used for diagnostic purposes in animals affected by glanders; I shall return to this subject in describing the diagnosis. The other substance, *morvin*, was obtained by A. Babes from bouillon cultures and is said to have a toxic action, but, besides this, also possesses immunizing properties.

From cultures of glanders bacilli, a number of different animals may be more or less readily affected by inoculation. It must, however, be remembered that if the bacilli of glanders are grown upon artificial culture media from generation to generation they lose their virulence after some time. If it is desired to retain the property of infection in cultures it is necessary to inoculate animals from the cultures now and then, obtaining new cultures from

the animals thus infected. Most susceptible to infection are guinea-pigs and field mice, then goats, horses and mules rank next. Less susceptible are rabbits and house mice, whereas cattle show themselves very refractory to inoculation.

I shall briefly call attention to the *phenomena of inoculated glanders in guinea-pigs*, as these animals, on account of their great susceptibility to inoculation with the bacillus of glanders, are used for diagnostic purposes. In guinea-pigs after the subcutaneous inoculation with glanders bacilli a cutaneous ulcer first develops at the point of the infection, soon being followed by swelling and later by suppuration of the regional lymph glands. Later, glandular nodules appear upon the nasal mucous membrane and suppuration occurs in the joints, in female animals in the mammæ and in the vulva. In male animals the very characteristic swelling of a glanders infection of the testicles often develops early, inflammation occurs followed by suppuration in the tunica vaginalis, which later attacks the testicle.

These changes in the testicle may be observed in from two to three days if the infectious material is injected intraperitoneally into the male guinea-pig, and Strauss has advised, therefore, infecting the animals in this way, if we desire to obtain a rapid diagnosis. For this purpose the injection should be made into the middle of the abdomen, for only then can we be certain that the injected fluid does not find its way into the very large and very motile *vesiculæ seminales*. If this is the case, even if only pyogenic organisms are contained in the inoculated matter, a swelling of the testicles may develop which may simulate glanders. But even if the injection is made with the proper precaution, the appearance of swelling of the testicles in guinea-pigs is not an infallible sign of glanders. I shall return to this when describing the diagnosis. Occasionally, even in the presence of the pathogenic agent of glanders in the injected fluid, the swelling of the testicles may not occur in guinea-pigs.

Guinea-pigs perish in from two to four weeks after the inoculation. Post mortem it is found that the internal organs are affected by glanders, especially the lungs and often the enlarged spleen shows various grades of enlargement, often yellowish nodules. In the younger nodules the glanders bacilli are present in greatest numbers, as well as in the secretion coming from the ulcers which have formed and also in the contents of abscesses and in the lymph glands.

I will now briefly call attention to the *symptoms of glanders in the horse*. These must be known to the practical physician, as the horse affected by glanders is the chief source of infection for man, and in the diagnosis of human glanders the determination of the fact that the patient has been in contact with animals affected by glanders is of the greatest importance.

In the horse, in about 90 per cent. of the cases, glanders runs a chronic course, the duration of the affection even attaining several years. It begins usually in the form of nasal glanders, which is characterized by the appearance of small nodules surrounded by a reddish areola, usually upon the mucous membrane of the septum narium and upon the nasal muscles, which soon change into ulcers with a lardaceous base and raised borders. These ulcers gradually become larger and occasionally may heal, forming radiating, or

elongated cicatrices. These phenomena are accompanied from the onset by the appearance of a mucoid, later yellowish, sometimes discolored, and occasionally even bloody nasal secretion, which may even be unilateral, and at the same time there develops at the onset a doughy, later becoming hard, indolent swelling of the glands of the larynx. Besides the symptoms of nasal glanders which by no means need always be present, there is often fever of an intermittent and remittent character, and if the disease implicates the deeper portions of the respiratory apparatus, cough and expectoration are present; now and then hematuria has been observed. As a rule, the animals emaciate in the course of the disease, and edema often occurs. More rarely in chronic glanders in horses there is an appearance of glandular changes in the skin, the so-called "worm" (button), in the form of more or less large, not painful nodules, which have their seat preferably on the extremities, in the thoracic and abdominal regions, which may disappear without leaving a residuum, but for the most part suppurate, forming slowly healing sinuous ulcers. As a rule, the lymph vessels and lymph glands are also attacked; they are swollen, hard to the touch, and occasionally suppurate, the first named forming thick strands, the so-called worm strands, which occasionally also suppurate. Sometimes chronic glanders in the horse may produce symptoms that are so slight that the affection can only be diagnosticated by veterinarians after a longer observation of the animal.

Acute glanders, which is more frequent in asses and mules, shows the same symptoms as the chronic form, accompanied by high fever and terminating fatally in from three to fourteen days.

Transmission of the bacillus of glanders to human beings is fortunately very rare lately; in bacteriologic work with these microorganisms earnest advice is given to be exceedingly careful. Occasionally transmission occurs *from man to man*, partly directly from nursing or from the autopsy of anthrax patients, partly also indirectly by fomites that have been infected by the secretion of glanders patients, as from clothing, drinking vessels, etc., but even these are exceptions. As a rule, as already mentioned, glanders is almost exclusively transmitted from animals, especially from horses, to man and this explains why particularly persons are affected who on account of their occupation, come in contact with horses, such as coachmen, hostlers, horse butchers, tanners, cavalrymen, farmers, veterinarians, etc., and as these occupations are for the most part all carried out by the male sex, glanders in women is of very rare occurrence. In general, glanders is not frequent in man, especially in those countries in which the dissemination of glanders among animals is controlled by laws, according to which persons are compelled to kill animals affected by glanders or those that are supposed to have glanders, and to render the cadaver innocuous. This has led to a great diminution of the affection. Another reason for the rarity of glanders in man is due to the fact that the human subject is not very susceptible to glanders infection.

The pathogenic agents most frequently enter by way of the *skin* and the *mucous membrane*, and they find their way into wounds that are already present or are transmitted by means of infected substances which produce injury to the skin or mucous membrane. In my opinion, it is not proven that also in man the entrance of the bacillus of glanders is possible through

the intact skin and mucous membranes, neither by the observation that the transmission of glanders to man without a determinable wound has taken place by contact with animals affected by glanders, nor by the experimental development of glanders infection, which Cornil and Babes produced in guinea-pigs by rubbing in glanders bacilli upon the undamaged skin and mucous membrane of the nose and conjunctiva; I do not believe that it can be overlooked, that here and there the smallest defects exist which escape observation, and these form the port of entrance for the bacilli.

The invasion of the bacillus through the *lungs* in man has not yet been definitely proved. Some observations seem to favor the appearance of an inhalation glanders in pulmonary disease of the lungs, but this occurrence is extremely rare.

Lately J. Koch (Archiv f. klinische Chirurgie, Bd. lxxv) has described a case of this kind which was also interesting in other respects. It was probably produced by the breaking of a tube containing a culture of glanders, and its contents spread in the workroom of the patient. According to the clinical phenomena, and also according to the autopsy, it was probable that the primary localization occurred in the lungs, so the virus was probably taken up with the respiratory air. The diagnosis of glanders was determined with certainty by cultures and by inoculation experiments.

Although a number of celebrated veterinarians have opposed the view that primary pulmonary glanders occurs in animals, the experiments of Babes prove that guinea-pigs may be infected by the inoculation of pulverized cultures, that an infection by way of the lungs is possible. It is true this form of transmission only occurs under very special circumstances, for other experimenters, such as Cadéac and Malet, had purely negative results in this direction.

That the *gastro-intestinal tract* may be the point of entrance for the bacillus of glanders has, as I believe, not been unobjectionably demonstrated, thus, by the observation of glanders in animals, which in zoological gardens and in menageries have been fed with meat infected with glanders, for the bacilli in these cases may have entered the mucous membrane through small wounds which may have been caused by chewing the bones; this mode of transmission must be doubted in view of the experiments of Decroix upon himself, who even ate the raw meat of animals affected by glanders upon several occasions without becoming ill. In spite of this, the use of even cooked meat should be prohibited under all circumstances, as even in cutting up and preparing the meat infection may readily occur.

Individual cases make it probable that infection may occur in women by way of the *genital organs*.

PATHOLOGY

The *pathological changes* observed in human glanders coincide in general with those occurring in animals, particularly in horses. In man new structures also develop in the tissues that are infected by the bacilli of glanders, which consist of leukocytes and epithelioid cells, which do not, however, contain giant cells and soon show a purulent decomposition, forming pustules, and later abscesses, which, if they are superficially situated, and the pus

discharges externally, may develop into ulcers. These new structures partly have the form of nodes and nodules, partly that of diffuse infiltration; in man infiltration usually becomes prominent. In the diseased tissue, especially in a recent affection, the bacilli may be found. They are more readily obtained in smear-preparations than in sections. I have already mentioned the best methods of staining. Only in rare cases are the bacilli found in the blood in man; occasionally a decided leukocytosis is present. The bacilli are rarely found in the urine; on the other hand, they are frequently present in the lymph glands which are in the neighborhood of diseased organs.

I shall briefly describe the changes in individual organs of the human subject produced by glanders.

Upon the skin, pustules and abscesses are found, which are not infrequently hemorrhagic, also ulcers with thickened margins and purulent, often discolored secretion, further erysipelatous, phlegmonous and gangrenous hemorrhagic processes are noted. These cutaneous changes may occasionally be accompanied with an inflammation of lymph vessels which may also go hand in hand with the formation of nodules, further, with suppuration of the lymph glands and also with inflammation of the veins, and in this connection, thromboses may develop.

Upon the mucous membranes there are found, besides inflammatory changes and occasionally hemorrhages, partly miliary and submiliary nodules of grayish appearance which sometimes attain the size of a pea or are even larger, partly larger and smaller pea-like prominences, partly ulcers of various sizes with raised borders, occasionally reaching to the bone or the cartilages, and these structures may also become necrotic. The nasal mucous membrane, especially at the septum and at the nasal muscles is preferably affected, not rarely the mucous membrane of the secondary cavities of the nose is the seat of the affection. Thus, frequently, the mucous membrane of the larynx, the trachea, the bronchi, the mouth and the pharynx is affected. Apart from the implication of the periosteum of other organs, occasionally primary inflammatory and purulent processes may occur in this structure. Nodules and abscesses are frequently found in different muscles, somewhat rarer suppuration of the joints, or of their surroundings. In the lungs, besides areas of gray hepatization, more or less extensive infiltrated areas are found, besides gray or grayish-yellow nodules from the size of a millet seed to larger nodes of the same color, but this is much more rare. Sometimes the pleura is also affected, in which, besides inflammatory changes, hemorrhages and also nodules may be seen. In the enlarged liver, which may show fatty degeneration, and in the swollen, soft, usually dark-red discolored spleen, abscesses are rare, nor are glandular nodules and abscesses frequent in the testicles, the kidneys or the brain. The appearance of inflammatory changes in the meninges and spinal cord, and the finding of glandular nodules in the choroid are rare phenomena.

SYMPTOMATOLOGY

In man as well as in animals, especially in the horse, glanders takes an *acute* and a *chronic course*. The chronic course, however, does not develop from the acute but arises directly. On the other hand, the observation has

occasionally been made, that in the course of chronic glanders the symptoms of the acute disease develop and then the affection rapidly terminates fatally.

The period of incubation of acute glanders is usually from three to five days, but rarely is it shorter than this. In a number of cases, in which naturally the time of infection could not be determined with certainty, the duration of the time of incubation has been given as from two weeks to three months.

In an infection which takes its point of origin from a cutaneous wound, there develops first at the point of entrance of the pathogenic agent an inflammation which soon becomes an ulcer and which gradually enlarges. The ulcer shows a lardaceous base and dark red, fissured, somewhat raised borders; the surrounding of the ulcer is for the most part inflammatorily changed, reaching to a wide extent, and not rarely in these inflamed cutaneous areas the eruption of vesicles and pustules may be seen, sometimes even the appearance of gangrene is noted. Often an inflammatory change of the lymph vessels, in the form of red striæ or bands, which are painful upon pressure, shows itself in the surrounding cutaneous area, and this may often be followed to the neighboring lymph glands which, as a rule, are swollen and sensitive to pressure. More rarely inflammation of veins is an accompanying phenomenon, as a result of which thromboses may occur.

During the development of the local changes which last about a week, a number of other symptoms may be observed in the patient, such as headache, weakness, slight sopor, anorexia, nausea, vomiting, further, pains in the muscles, especially in the legs and in the joints. High fever is commonly present, which often begins with a chill. These symptoms may be present before the local changes occur.

In the second week the eruptions upon the skin appear, their seat being entirely independent from the point of entrance of the bacilli. They vary from diffuse, soft swellings, which show no redness and are not painful and may soon suppurate, the pus often discharging externally and giving rise to ulcers, to hard nodules which are characterized by their sensitiveness to pressure and their redness and which also soon change to ulcers. The ulcers which develop in this manner often invade the deeper structures, so that muscles, tendons and bones are laid bare. These exanthems show a preference for the extremities. The muscles themselves frequently show nodules or abscesses which have developed from them. Suppuration of the joints and their surroundings has also been observed.

Besides these eruptions, at about the same time or even later, associated with hemorrhages, small red spots appear, which soon rise above the skin and become papules; they do not remain long in this condition but soon change to pustules which show no umbilication and at first have the size of a hempseed. The development of the macule into the pustule may occur in a very brief time, in a case observed by me it arose overnight. The number of pustules varies greatly in individual cases; while in a number of patients they may be only isolated, in others the entire skin may be covered by them. Often they are arranged in groups and by confluence they develop larger pustules. The pustules rarely dry, as a rule, but form ulcers from which, occasionally, erysipelatous and gangrenous processes arise.

In a number of cases these changes upon the skin are accompanied with

eruptions on the nasal mucous membrane. These may be the first symptoms, if the bacilli have found their point of entrance in the nasal mucous membrane. Their appearance is shown by the fact that the patient complains of a "stuffed" nose, the speech being nasal and a thin white secretion flowing from the nose, which secretion later on becomes tough and yellowish, occasionally being mixed with blood, and which is very offensive. If the nasal mucous membrane is examined it is found inflamed, covered with nodules, and infiltrations or ulcers which have developed from them, which occasionally may reach the bone and cartilage giving rise to necrosis in these structures. Some patients also complain of frontal headache, which is due to glandular changes of the mucous membrane of the cavities of the frontal bone, and in a similar manner the mucous membrane of the cavities of the nose may also be affected.

Frequently the nasal affection is complicated by swelling, painfulness upon pressure and also by an erysipelatous inflammation of the skin at the root of the nose. This inflammation may develop over the entire face, running its course by the formation of vesicles, ulcers and gangrene.

Inflammatory and ulcerative changes may also be noted upon other mucous membranes, which occur simultaneously with another affection or follow it. Thus, upon the gums, besides hemorrhages, the phenomena of inflammations and not rarely ulcers are noted. The tongue, which for the most part has a more or less decided coating, is covered upon its posterior aspect with ulcers, as are also the usually enlarged tonsils, so that the patients have difficulty in taking food, which difficulty may even be decidedly increased if inflammatory changes are present upon the floor of the oral cavity, and the submaxillary, sublingual and parotid glands are implicated in the affection.

The appearance of hoarseness or aphonia points to an affection of the larynx, and if the patient is examined with a laryngoscope, not only redness and swelling of the mucous membrane but sometimes even characteristic eruptions are present. The swelling of the mucous membrane of the larynx also explains in some cases the difficulty of respiration which occurs, but in the majority of cases this is due to changes in the lungs, which arise as the result of glanders. The dyspnea is then accompanied with sensations of pressure and pain in the chest. Upon an examination of the lungs, as a rule, râles and dulness may be demonstrated, and sometimes the pulmonary affection is complicated by pleurisy, which may be either dry or show an effusion. Cough and expectoration are then never absent; for the most part the cough is frequent, and the expectoration has a muco-purulent consistence, may contain blood and has a fetid odor.

Not rarely are there symptoms on the part of the gastro-intestinal tract, and to the anorexia, nausea, and the vomiting, which appear at the onset of the affection, there is added diarrhea which may become very copious. Constipation may precede the diarrhea. Jaundice is rare. The liver and spleen are enlarged. In but few cases is there an enlargement and a sensitiveness to pressure of the testicles. Albumin and casts may appear in the urine; the appearance of bacilli is but exceptionally observed. Worthy of note is the appearance of the diazo-reaction in the urine, as was noted by Strube, in one case.

I have already mentioned that glanders in man appears with high fever, only in rare cases is it introduced with a chill. In the further course of the disease chills may occur especially when pustules, ulcers or abscesses have formed, they may then even become frequent. Occasionally a gradual ascent of the temperature may be observed; but the course of the temperature may show different conditions, a continued, a remittent, and an intermittent fever occurs, but for the most part it is atypical. High temperatures, especially toward evening, are predominant; but I must also call attention to the fact that at the onset of the affection fever may be absent entirely.

Prior to death, besides cardiac asthenia, comatose conditions, delirium and convulsions occur. The acute form of the affection is almost always fatal, recovery is extraordinarily rare. The duration of the disease is usually from two to three weeks. In some cases death occurs only after five weeks, or even later, and, on the other hand, the affection may last but a week, but this is exceptional.

Chronic Glanders.—The duration of the affection varies; most cases run a course of from four to five months; individual cases may last for a year or more and cases are found in literature in which the course of the disease extended over eleven and even fifteen years. The symptoms which are observed in chronic glanders coincide in the main with those of the acute form. The development of chronic glanders is insidious, especially in those cases in which the point of entrance of the bacilli remains unknown. In these cases the disease begins with fever, but this is by no means always the case. As a rule, a constitutional disturbance ushers in the disease, a number of patients complain of headache, lassitude, loss of appetite, occasionally pains appear in the muscles, often also in the joints, and then sometimes swelling is noted in these regions; only after from five to six weeks do there develop upon the skin or upon the mucous membranes, especially that of the nose, the phenomena which are so characteristic of glanders, which are in the main the same as in the acute affections, but which for the most part show a protracted course.

In chronic glanders which occurs in connection with a wound that has been infected by the bacilli of glanders, after from three to four days the first symptoms appear at the point of infection; these symptoms and those which occur further on at the seat of the lesion and in its surroundings correspond to the changes that have been described in acute glanders, only the appearance of these symptoms is distributed over a longer period. The changes observed at the point of infection and in its surroundings are in the main those of an enlargement of the regional lymph glands, often accompanied with fever, lassitude, headache, loss of appetite, muscular and arthritic pains. Cases have been observed in which only these symptoms develop, they may last for many months, and occasionally with suitable treatment improvement and recovery may occur.

A case is known to me in which the affection remained limited to the upper extremity, and besides the changes at the point of infection upon the hand, only enlargement and suppuration of the lymph glands at the elbow joint appeared; fever and constitutional disturbance were absent. The diagnosis was certain in this case, for, apart from the fact that the affection

occurred a few days after assisting at the autopsy of a patient that died of glanders, the bacillus of glanders was found in the pus of the lymph glands in a bacteriologic investigation. With surgical treatment recovery occurred in two months, and proved to be a permanent one.

It is more frequent, however, that after a longer time has elapsed since the appearance of the first symptoms eruptions develop on the skin distant from the point of infection, similar to those which occur in the acute form. Naturally, in chronic glanders the nodes and abscesses in the skin, the subcutaneous tissue, and the muscles are prominent. At the onset they are usually few, only gradually increasing in number. Their points of selection for their development are the extremities, especially the lower extremities. The abscesses then rupture through the skin and thus sinuous and fistulous ulcers develop which sometimes may cicatrize. On the whole, the tendency to healing is but very slight in them, for the most part they extend and may give rise to great destruction in the skin. Periodically a marked improvement may be observed in the patient, the fever that is frequently present disappears, the symptoms which accompany the disturbance of the skin cease, but for the most part this is only transitory. A rise in temperature, the eruption of new nodules, and the development of new abscesses shows us that the disease has not disappeared. Thus, it may occur that improvement and relapses alternate, and cause the disease to be protracted for a long time, even for many years.

In chronic glanders changes on the part of the nasal mucous membrane also occur, but this happens only in about one-half of the cases. They may develop simultaneously with rashes of the skin, but may also precede them. Occasionally they are even present without symptoms being observed in the skin. In the main they show the same clinical picture and present the identical accompanying phenomena to those of acute glanders, only the phenomena show a more protracted course. Not rarely do changes, which are characteristic of glanders, occur in the mucous membranes of the mouth, pharynx, and larynx. In spite of the distribution of the disease to these mucous membranes, in the course of time even after the affection has existed for years recovery may occur. Naturally, this favorable course must be excluded if symptoms are present which point to an implication of the internal organs, especially of the lungs, the gastro-intestinal tract and the kidneys. Under these circumstances, sooner or later the lethal outcome occurs. This may be hastened if in connection with chronic glanders the acute form appears, which then runs a fatal course in from two to three days. It must still be mentioned that glanders is complicated by pyemic phenomena.

PROGNOSIS

According to Bollinger, about one-half the chronic cases of glanders terminate in recovery. It results from this that the *prognosis* from chronic glanders is not considered to be so unfavorable as that of the acute form in which the fatal outcome is practically certain in almost all cases. Nevertheless, chronic glanders is a disease which must always be looked upon as serious. In chronic cases the development of acute glanders must be considered, which in a very brief time may terminate the life of the patient. A favorable course

in acute glanders is to be hoped for when the cutaneous and mucous membrane exanthems do not show great distribution, when the internal organs are not implicated in the disease and the constitutional condition of the patient remains good for a long time.

DIAGNOSIS

As will have been gathered from the description, the clinical picture of glanders may vary greatly according to whether the individual organs are implicated in the morbid process; for this reason the *diagnosis* in glanders, often quite difficult, and especially so when the etiologic conditions are not quite clear. These difficulties may be especially prominent at the onset of the disease in those cases which begin with fever, lassitude, and anorexia, and in which the local phenomena on the part of the skin and mucous membranes are absent for a time. Then a confusion with other acute infectious diseases, especially with *enteric fever* or *influenza* is easily possible, and when the pains in the joints become prominent and if decisive swelling occurs in these regions the affection may be mistaken for *acute articular rheumatism*. Only in the further course when the characteristic changes on the part of the mucous membrane or of the skin appear, and the investigations directed to these points show an infection with the virus of glanders, is the disease correctly diagnosed. Even when acute glanders, after the entrance of the pathogenic organism into a cutaneous wound, begins with local phenomena the differentiation from an *infection with pyogenic organisms* which may run a course with similar phenomena, gives rise to difficulties, and these may continue to exist if in connection with a suppuration a *septicopyemia* develops, for in acute glanders abscesses and fever are not rarely predominant symptoms, and chills are also frequently observed. Also in these cases only after the changes in the nasal mucous membrane have developed further and the history has been obtained will the diagnosis become clear. It is quite certain that some cases of glanders are taken for ordinary suppurations. That this is easily possible was clear to me after the case that has already been mentioned of the undertaker who infected himself at the autopsy of a man that died of glanders. In this patient, besides changes at the point of entrance, only swelling and, further on, suppuration of the lymph glands in the elbow joint developed. If in the course of the disease the source of infection had not been known, and for this reason the bacillus of glanders was searched for in the pus and the proof of its presence had been successful, an ordinary case of suppuration would have been supposed to exist.

Confusion of glanders with *anthrax* may easily be excluded, this has been mentioned in the diagnosis of anthrax.

The recognition of chronic glanders may be very difficult, especially if the etiologic conditions are unknown. Cases are known that were carefully observed for months and in which the diagnosis was only made at the autopsy. In the *differential diagnosis* of chronic glanders, especially *tuberculosis* and *syphilis* must be considered, for the ulcers of the skin and mucous membrane in glanders, in many respects, show a similarity to tubercular and syphilitic ulcers. The combination of changes of the mucous membrane, especially of the nose, with cutaneous eruptions, particularly the appearance of abscesses,

the presence of severe clinical symptoms, is in favor of glanders. In favor of syphilis is the simultaneous appearance of other phenomena characteristic of syphilis and the prompt relief after administration of mercury and iodid of potassium. It is true, a favorable influence is ascribed to these remedies also in glanders; however, they act far more slowly as a rule. On the other hand, the demonstration of tubercular changes in the internal organs, especially of the lungs, the finding of tubercle bacilli in the ulcers, will especially ensure the diagnosis of tuberculosis.

In chronic glanders, as well as in many doubtful cases of acute glanders, the affection will only be properly recognized upon the basis of the bacteriologic investigation of the secretion of the ulcers or of the pus from abscesses. A certain decision cannot be reached alone by the aid of staining methods, for the bacilli cannot be differentiated, neither by their tinctorial nor by their morphologic properties from similar microorganisms which not rarely occur side by side with them in the secretion of ulcers or the pus of abscesses. For this reason, it is necessary that cultures be made and inoculation practised in animals that are very susceptible to glanders.

It is best to make inoculation experiments, and for this purpose guinea-pigs are most used, field mice also react well to the inoculation of glanders but they are difficult to procure. If guinea-pigs are used, a few days must elapse before it is possible to obtain results. I have also called attention to the fact that after inoculation of infectious material into the guinea-pig, in from two to three days a swelling of the testicle occurs, primarily in an inflammation of the tunica vaginalis which terminates in suppuration, which may later also extend to the testicle; for this reason Strauss has advised that a sufficiently large amount of material which is suspicious of glanders be floated in sterile water and intraperitoneally injected into guinea-pigs in order to arrive at a rapid diagnosis. It is, however, necessary, a fact to which I have already called attention, that the fluid be injected into the middle of the belly, otherwise the fluid may enter the very large and motile seminal vesicles of the guinea-pig and then if pyogenic agents are present a swelling of the testicle resembling that of glanders may occur.

It is true, even if the bacillus of glanders is present in the fluid injected intraperitoneally, that swelling of the testicles may not occur. On the other hand, even if the injection is made in the median line and a swelling of the testicle occurs, this does not absolutely prove that the material used for investigation contains the anthrax bacillus, even if bacilli morphologically resembling anthrax bacilli are noted in the pus and the autopsy of the animal shows a condition which is common to glanders. Kutscher found, in the nasal secretion of a horse affected by glanders and Nocard found in a case of purulent lymphangitis in a horse, bacilli which in their morphologic properties coincided completely with the bacilli of glanders, and even after an intraperitoneal injection into a guinea-pig produced the same changes in the testicle that occur in glanders. Even the autopsy of the animals which perish after infection with the bacillus showed many similarities to glanders. These bacilli could, however, be differentiated from the bacilli of glanders, in that they showed other properties in cultures and also that they stained according to Gram, whereas the bacilli of glanders, as is well known, do not stain according to this method.

In consequence of this, if Strauss's process gives a positive result it will be necessary by the aid of Gram's method and culture processes to test the bacilli which are found in the pus of the testicles, and also in other diseased organs, to determine positively that they are bacilli of glanders.

Regarding *mallein*, in so far as the very few results show at present, not much is to be expected as a diagnostic aid in human glanders.

TREATMENT

As glanders is such a serious affection, against which, especially in its acute form in man, therapeutic measures are powerless, special stress must be laid upon *prophylaxis*. In this direction nothing can be accomplished unless glanders in the horse, which is the almost exclusive source of infection for human beings, is limited to the utmost possible extent. In different countries laws have been passed for this purpose, thus in Germany a law dated June 23, 1880, and one dated May 1, 1894, and another June 27, 1895, enforce the killing of all animals affected with or supposed to have glanders, also the destruction of their cadavers by great heat or by chemical means. For this it is necessary that glanders should be diagnosticated in animals as early as possible. The diagnosis, especially of chronic glanders, however, is often very difficult, and especially in the horse in which it runs a chronic course, not infrequently even being latent. Especially in these cases the bacteriologic investigation of the secretions from the nose, pus from abscesses, etc., which are to be carried out in the manner just described in the diagnosis of human glanders, offer an important diagnostic aid. There is no unanimity of opinion among veterinarians regarding mallein in the diagnosis of glanders in the horse; whereas a number assume that mallein has shown itself as very useful in this direction, others deny its importance or value as a diagnostic aid.

I believe it is especially important to acquaint all those who in their occupations come in contact with horses as thoroughly as possible with the principal symptoms of glanders, and they should be advised to consult a veterinarian at once in any suspicious case. Further, all those that come in contact with man or animals affected by glanders should be advised of the danger of contagion so that any possible wounds may be covered by suitable bandages, and their hands thoroughly disinfected with a 1 to 1,000 solution of corrosive sublimate. All materials that come in contact with the secretions of the sick, even before the infectious secretions have had an opportunity of drying should be disinfected either by the prolonged action of boiling water or steam, or with a 1 to 1,000 solution of corrosive sublimate.

Wounds infected with the virus of glanders are to be disinfected first with a 1 to 1,000 solution of corrosive sublimate, followed by the application of the thermo-cautery. A favorable action, however, is only to be expected in cases in which this treatment is applied shortly after infection has occurred.

Patients with glanders are to be isolated. The point of injection upon the skin is best treated with the thermo-cautery. The nodules and abscesses are to be opened as early as possible, the abscess cavity to be scraped with a sharp curette, cleansed with a 5 per cent. carbolic acid solution or a 1 to 1,000 corrosive sublimate solution and dressed with iodoform gauze. Phlegmonous changes in the skin are to be treated with poultices of acetate of aluminum.

In the treatment of glanders of the nose, frequent spraying of the nose with solutions of potassium permanganate or carbolized water or insufflations of iodol or aristol or a mixture of iodoform and tannic acid in equal parts, remedies which are also used to advantage in the mucous membrane of glanders. Garré noted an especially favorable action on the ulcers of the nasal mucous membrane by cauterizing with zinc chlorid.

We have no knowledge of a remedy that is positively active in glanders.

The use of potassium iodid for a long period and inunctions of gray salve (4 grams daily) is worth a trial in chronic glanders. The treatment by mercury has favorably influenced some few cases; however, there are numerous reports of failures regarding this method of treatment. No positive opinion can be formed regarding the action of mallein in the treatment of glanders, as until this time the remedy has been too little employed.

In the main the treatment of glanders is symptomatic. Suitable nutrition, the use of strengthening remedies and alcoholic drinks should be employed in order to maintain the powers of the patient as long as possible.

FOOT AND MOUTH DISEASE

BY A. NICOLAIER, BERLIN

Foot and mouth disease or the aphthous plague (aphthæ epizooticæ) is an acute infectious disease, and it also, as well as anthrax and glanders, belongs to the zoonoses, for, the same as those diseases, it is transmitted almost exclusively from animal to man, and in the human subject shows the same or similar symptoms to those occurring in the affected animal.

In *man* the disease is not so infrequent as has been assumed up to now. Although the number of cases in literature since the seventeenth century, which have been collected by Siegel and Bussenius amount to 140, this not being a large number for this period, it must be remembered that this figure only represents the very smallest fraction of the cases of foot and mouth disease which have actually occurred, for only a small number of the cases that occur are made public. It is quite certain that a large number of cases in which the symptoms are not developed in the characteristic manner, and especially in which the anamnestic data regarding infection with the virus of foot and mouth disease cannot be obtained, are not diagnosticated as foot and mouth disease, and, finally, quite a large number of cases, especially those that run a mild course, do not come under the observation of a physician.

Foot and mouth disease occurs particularly in cattle, further, in the sheep, the pig and the goat, in rare cases in the dog and in the cat, and now and then in poultry. The disease distributes itself rapidly by direct transmission or also through the agency of those who tend cattle, or from stalls that are not sufficiently disinfected or by fomites—especially by fodder—which has been contaminated by the infectious secretions of sick animals, spreading from animal to animal and in a very brief period affecting extraordinarily large numbers. The damage which this disease causes to farmers, on account of the deaths which are especially frequent in virulent epidemics, by the loss of milk and milk products, by the reduction in the weight of the animal, by the loss of labor performed by the animal, which is often considerable on account of the prolonged sequelæ which occur in these animals, further, by the laws enacted requiring isolation which paralyzes trade, is very large and yearly amounts to many million dollars.

In *cattle* the disease begins in from three to five days after infection, with fever, which often rises to 104° F., with increased salivation and an inflammation of the mucous membrane of the mouth, upon which in about two to three days, small vesicles develop which are at first filled with yellowish, clear contents which later become more and more turbid. These vesicles gradually increase in size and rupture in from one to two days, thus, small erosions or ulcers appear upon the mucous membrane which, as a rule, heal in the course

of a week. The same changes may occur, even though rarely, upon the nasal mucous membrane, or surrounding the nasal opening, as well as upon the mucous membrane of the conjunctiva, and the vagina, upon the udder and the teats.

The mammary gland itself may be affected. Simultaneously, sometimes before the eruption upon the mucous membrane, especially that of the oral mucous membrane, there develops upon the skin, in the region of the crown of the foot, and in the spaces, a very painful inflammation, which is followed in from one to two days by the eruption of vesicles, which in appearance and in their further course correspond to those occurring upon the mucous membranes. These changes may also occur in other areas of the skin. The constitutional condition of the animals often suffers severely; they have such loss of appetite that they become emaciated and the secretion of milk diminishes; older animals withstand the affection, which in them runs its course in from eight to fourteen days. If severe complications occur, such as pneumonia, gastro-enteritis, a lymphangitis extending from the hoof, phlegmons, erysipelas, purulent arthritic inflammation, pyemia, or extensive ulcers, which is especially the case in malignant epidemics, the affection lasts much longer, and not infrequently leads to a fatal outcome.

In *sheep*, in the *goat* and in the *pig*, the affection localizes itself particularly to the hoof, in the *horse* only the mucous membrane of the mouth is affected.

That foot and mouth disease is *transmissible from animal to man* and that the milk of animals may be the carrier of the infectious product, we have known since the end of the seventeenth century; however, it was only unmistakably proven in 1833 by the experiments of Hertwig and his assistants upon themselves, who developed foot and mouth disease after the use of raw milk taken from infected animals. By the transmission of foot and mouth disease from man to animal, which was successfully accomplished in 1893, the definite proof was established that the same pathogenic agent is active in man as well as in animals.

In spite of the numerous attempts that have been made to clear up the *etiology* of this affection, the infective agent is still unknown. But after the investigations lately carried on by Löffler and Frosch, there can scarcely be a doubt that the microorganisms which have been noted by their discoverers to be the cause of the disease, such as Klein's micrococcus, the streptocyte of Schottelius, the streptococcus involutus of Kurth, the ovoid bacterium of Siegel, the protozoa-like structure of Behla, and other microorganisms, bear no causal relation to foot and mouth disease. Owing to the important investigations of Löffler and Frosch, we have become acquainted with a great many of the properties of the pathogenic agent of foot and mouth disease.

Regarding the virus of foot and mouth disease, of which, as Bollinger assumes that it may also be volatile, we have known for a long time that it is present in large amounts in the vesicles, or in the vesicles of the ulcers of the mucous membrane and of the skin, in man as well as in animals, further, that it may be found in the saliva, in the milk, in the urine and in the feces. The virus is also present in the blood of the affected animal, naturally, only from the time of the rise of temperature until the appearance of the local eruptions. It appears that the pathogenic agent may even then occur in the blood but in

much smaller amounts. As shown by Löffler and Frosch, the smallest quantity of the contents of the vesicles is sufficient when injected intravenously, intraperitoneally, or by intramuscular injection to produce foot and mouth disease in cattle or calves. Other animals, especially sheep and goats, in which the disease also occurs spontaneously, do not react to inoculation. Subcutaneous injections only act with certainty if blood vessels are injured. In cattle, and especially in the calf, it is sufficient to infect them if sponges soaked with the secretions from the mouth of the affected animal are placed in the mouth of the well animal, and although this has not succeeded in all cases, infection was always produced provided the mucous membrane was previously scarified. Infection is also easy by way of the gastro-intestinal tract.

According to the investigations of Löffler and Frosch the infectious agents of foot and mouth disease must be extraordinarily minute microorganisms, for they pass through porcelain filters which even retain the smallest microorganisms. Attempts to cultivate them upon the usual bacteriologic culture media have not been successful, but they can be caused to multiply in the animal organism, as animals that are inoculated with lymph from which the bacterium was filtered transmitted the disease to other animals, and even from these inoculation was successful in others.

Upon the basis of investigations, it has been assumed in regard to the virus, that its virulence is retained for a longer time, being capable of infecting after remaining in stalls and especially in dung, for several months. This resistance of the poison may account for the fact that the disease may very readily be transmitted even to greater distances, and this transmission occurs particularly by the secretions and excretions of affected animals, that is by fomites infected by them, such as materials used in stalls, dung, fodder, occasionally even transmission may occur through the agency of human beings. Accurate reports regarding the resistance of the virus of the infection of foot and mouth disease are only known to us since the investigations of Löffler and Frosch which they have attained in an exact manner. I shall limit myself here to emphasizing that the fluid of the vesicles upon the mucous membrane, if saved in glass capillary tubes and placed in an ice chest, only begins to lose its activity after three weeks, that it may even still be infectious after eight to nine weeks. If the lymph is free from bacteria it may even remain virulent for from three to four months. On the other hand, the virus contained in the vesicles is destroyed in twenty-four hours at a high summer temperature. It is very susceptible to the influence of heat, the action of a temperature of 60° C. for a half hour diminishes the virulence of the virus decidedly, and at a temperature of 70° C., in the same time it is completely destroyed. For this reason, the prolonged action of the temperature of boiling water is the best means of rendering the virus harmless, especially in milk.

In regard to the behavior of the virus toward disinfectants, it is only known that the usual substances destroy it after an action of one hour. Cleansing the hands with soap is not sufficient for proper disinfection, but this is readily attained by the use of carbolyzed water.

For man the most frequent source of the disease is the milk of affected animals. I have already stated that the transmission to man occurs through the use of raw milk of affected animals, as Hertwig's experiments upon him-

self and his assistants have proved beyond doubt, besides numerous observations have shown that not only raw but even insufficiently cooked milk, may be the carrier of the infection. Even if the milk from infected animals is mixed with a large quantity of normal milk, the infective property is not lost. Some investigators assume that the raw milk of affected animals does not always contain the virus. It is said to be particularly infectious during the time of the fever, the virulence declining as the temperature disappears; especially is it thought to be harmless when the udder and teats are not implicated in the disease, so that the milk does not become contaminated by the contents of the vesicles or by the secretions from ulcers. In any case, the milk from animals affected by foot and mouth disease is not to be used, for even if it be possible, as I have already indicated, that a sufficiently long boiling destroys the infectious agent in the milk, this process renders it unpalatable, and should not be used in the nutrition of children, as not only is the milk in foot and mouth disease diminished in quantity, but it also differs in many other ways from normal milk; it has a yellowish appearance, resembling colostrum, coagulates readily and quickly becomes sour, often has a tart taste, and shows a sediment which contains pus corpuscles; its quantity of salt is occasionally increased, the amount of casein, fat and sugar, however, being diminished. As the milk, so also the products obtained from it, cream, butter, cheese, etc., contain the pathogenic agent, as has been determined with certainty from investigation.

Upon sufficiently long cooking the meat of infected animals is probably rendered harmless, but the possibility of the transmission of the virus in handling the raw meat must be considered, and for this reason care must be practised in its preparation. Individual observations teach that in slaughtering sick animals, infection with the virus of foot and mouth disease has occurred if there has been an opportunity for the poison to enter wounds in the skin, and in the same way infection may occur in looking after infected animals, and particularly in milking, if the udder shows vesicles and ulcers. In all such instances, the cutaneous eruption in the human subject appears primarily upon the upper extremity.

Whereas in this manner of infection, defects in the skin are the points of entrance of the poison, a lesion of the mucous membrane does not appear to be a necessary requisite for the origin of the disease. This is shown by the experiments of Löffler and Frosch in animals, as I have already mentioned. These investigators succeeded in producing foot and mouth disease in cattle if the mouths of the animals were wiped with cloths or sponges in which the virulent salivary secretion was present. Naturally, some negative results prove that this manner of transmission is not as certain as if the mucous membrane had been previously scarified, that the virus adheres to the mucous membrane better provided this structure has been previously injured. Observations in man are also in favor of the fact that even with an intact mucous membrane, infection with foot and mouth disease is probable. In the main, however, man is but very slightly susceptible to the poison of foot and mouth disease, for even in very widely disseminated epizootics, in which, in spite of all possible prophylactic measures, he still has a plentiful opportunity of infecting himself, he is rarely attacked by the disease. Children are by far

more frequently affected than are adults. It is worthy of note that, similar to the case in animals, occasionally also in human beings, disease occurs in families, in individual houses, and even sometimes in extended epidemics, which, not infrequently, occur simultaneously with epizootics, when they may even show a malignant course.

I desire to call attention to the fact that *transmission* of the disease from *man to man* in nursing the sick, and, further, also by kissing, have been described. These cases teach that in man it is also advisable to adopt measures which prevent such contagion.

SYMPTOMATOLOGY

The first symptoms of the disease occur in man from three to five days after infection, however, cases have been observed in which the *period of incubation* is much longer, from eight to ten days, such as the observations of Siegel during an epidemic in the neighborhood of Berlin, which showed many peculiarities, not only as regards symptomatology, but also in the course of the disease.

The first symptoms are those of constitutional disturbance; lassitude, pains in the head and small of the back, in the limbs, further, pains in the gastric region, combined with nausea, sometimes also dryness and heat in the mouth, slight difficulty in deglutition, sometimes even vertigo and insomnia, these being the main symptoms of which the patients complain in the first days of the disease. The appetite is diminished, often complete anorexia is present, vomiting takes place and now and then epistaxis has been observed. These phenomena are usually accompanied with a rise in temperature to 103.1° F., which, however, rarely is preceded by a chill; in some cases the rise in temperature is slight, it may even be absent entirely, and these are by no means the milder cases in which this is observed, but also the severe ones may run an afebrile course.

If the infection has occurred by way of the *mucous membranes of the mouth and pharynx*, after a few days changes in these structures are noted. The first to develop are sensations of burning, redness and swelling of the mucous membrane of the lips, the cheeks and the tongue, which in mild cases may be the only symptoms. Generally, often in paroxysms, vesicles appear upon the inflammatorily changed mucous membranes, these containing watery contents which later become more and more turbid. These vesicles may gradually attain the size of a pea, or may even be larger and, by coalescence with neighboring ones, may form circumscribed vesicles. But very rarely do the vesicles appear on the mucous membrane of the hard and soft palate, the nose and conjunctiva. These eruptions remain from two to three days, they then rupture and erosions remain or ulcers are formed. As a rule, the ulcers are superficial, and for this reason heal without obvious scars. Rarely are ulcers resembling diphtheria observed, nor is it frequent that septic processes appear.

According to Ebstein, and this has been confirmed by Stierlin, in foot and mouth disease the formation of vesicles upon the mucous membranes may be absent, and instead of them grayish-white formations may appear

surrounded by an areola often attaining the size of a lentil and frequently developing into ulcers. These phenomena, as a rule, are accompanied by salivation and frequently the salivary, or the submaxillary glands are enlarged. Sometimes *fætor ex ore* is present.

These changes of the mucous membrane of the mouth and pharynx give rise to great difficulty on account of the pain caused by the erosions and ulcers, and this may even be increased if the tongue, which usually shows but a more or less decided coating, becomes much inflamed. Especially in chewing and swallowing solid food this may be so considerable that under these circumstances it is only possible to nourish the patient with fluid food. More extensive and more intense changes, especially if the mucous membrane of the nose and larynx is implicated in the disease, may give rise to difficulty in respiration. That the inflammatory swelling of the tongue, in foot and mouth disease, reaches such marked grades, that attacks of asphyxia may occur, is certainly very exceptional.

Besides the eruptions which occur on the mucous membranes in foot and mouth disease, the skin is also affected. Sometimes, by no means in all cases, eruptions appear, which in regard to their localization and characters are not always similar, occasionally being macular, at other times papular efflorescences, at one time resembling measles, at other times scarlatina; sometimes even urticaria appears. These exanthems may be distributed over the entire body, for the most part only circumscribed cutaneous areas are affected; as a rule, they appear before the eruptions on the mucous membranes, but they commonly remain after those upon the mucous membranes have developed.

Besides this, eruptions which are analogous to those upon the mucous membrane appear upon the skin simultaneously with the changes upon the mucous membrane. These are clear watery vesicles which occur in crops, similar to those upon the mucous membranes; they are usually distributed, rarely in groups, and soon contain turbid, later purulent contents, drying finally, and forming yellowish-green crusts. They but very rarely ulcerate. They occur particularly upon the upper extremity, especially around the fingers, about the nails. More rarely they are noted in the face, upon the toes, upon the nipples and upon the genitalia; according to the observations of Lewin, chancre-like ulcers are said to appear upon the genitalia as the result of foot and mouth disease. Occasionally these eruptions upon the skin are accompanied by erythema, inflammatory processes and suppuration, which in rare cases may develop phlebitis.

The cutaneous affections just described are not present in all cases, they may even be absent in cases in which the changes upon the mucous membrane are marked and very extensive.

If the infection with the virus of foot and mouth disease has its point of origin in *cutaneous wounds*, the course of the affection proceeds in the manner that first the constitutional disease develops, then the vesicles arise, primarily at the point of invasion. As infection in most of the cases occurs in slaughtering or milking sick animals, these eruptions are most frequently found in the upper extremity, especially upon the fingers. Besides, at the point of the affection, redness, swelling and painfulness appear, then the previously described exanthems develop upon the skin, which are distant from the point

of entrance of the virus, and then only do the phenomena on the part of the mucous membrane, sensation of burning in the mouth, difficulty in deglutition, redness and swelling of the mucous membrane, with the formation of vesicles and ulcers appear. Occasionally the mucous membrane may even remain free from changes.

The temperature usually falls and soon returns to normal with the appearance of the eruption upon the mucous membranes and upon the skin and if these appear in paroxysms this occurs with the last attack.

Complications on the part of internal organs are for the most part only noted in the gastro-intestinal canal; the patients have but little or no appetite, complain of pain in the abdomen, suffer from vomiting and severe diarrhea. These conditions are much more common in children than in adults.

In an epidemic of foot and mouth disease that occurred in human beings in the years 1888 to 1891 in the neighborhood of Berlin, Siegel noted a large number of complications and among these even severe ones. The course of these cases differed so decidedly from that usually observed in foot and mouth disease that it is certainly not strange that doubts arose whether this malady, appearing simultaneously with an existing epizootic, was in causal relation with it or whether it was not probable that it was produced by other causes than foot and mouth disease. Even Siegel admits that in the severest fatal cases, an infection from diseased animals in which the course of the affection was particularly mild, could not be demonstrated, and that those persons who were infected from the sick cattle showed but a mild disease.

Nevertheless, I desire to call attention to the most important phenomena that were observed in this epidemic by Siegel. As previously mentioned, the period of incubation in these cases lasted from eight to ten days, the attack began with chill and the other phenomena which are usually found in foot and mouth disease, but in these cases they appeared with a special severity. Besides decided swelling of the gums, loosening of the teeth, swelling of the bones of the jaw, especially of the lower jaw, tension in the masseter muscle, severe ear-ache, painfulness and swelling in the region of the liver, jaundice and paresthesia of the lower extremities were observed. Besides in a number of cases severe complications developed, a decided swelling of the tongue was noted so that it protruded beyond the inner border of the teeth and was so tightly jammed between them that a part of the tongue became necrotic. Ulcers appeared upon the gums, further, upon the mucous membrane of the nose, the throat and the gastro-intestinal mucous membrane. There were also observed catarrhal pneumonia, arrhythmic cardiac activity, albuminuria; and among nervous symptoms vertigo, attacks of spasm, hemiplegia, and stiffness of the muscles which even increased to tetanic rigidity. A number of patients after recovering from the affection remained cachectic for a long time.

PROGNOSIS

Then as regards the severity of the complications, in dealing with such malignant cases as those observed by Siegel, the chances for recovery are not favorable, and in such instances the prognosis becomes questionable. Fortunately, such a course of the affection is rare, and, apart from those cases which are also exceptional, in which septic processes develop upon the skin and upon

the mucous membranes, from suppuration which may even be the cause of a protracted illness, the majority of cases, at least in adults, usually recover in from two to three weeks. The conditions are different in childhood, and especially in infancy. Foot and mouth disease is a serious affection in children, for, apart from the fact that by an implication of the mucous membrane of the mouth and pharynx the intake of nourishment becomes difficult, sometimes even being impossible, symptoms on the part of the gastro-intestinal tract, which are by no means rare in children, may give rise to severe damage. As a result of this, the children emaciate rapidly, become weaker, and finally death occurs. For this reason, the prognosis in children, especially in infants, and particularly if the gastro-intestinal tract is implicated in the affection, must be doubtful.

PATHOLOGY

The *pathologico-anatomic changes* in foot and mouth disease have been described in the symptomatology, for they are particularly those of the skin and the mucous membrane. The few autopsies that have been made in foot and mouth disease, have shown a negative result in adults, outside of the changes in the skin and mucous membrane. Only in children are there complications relating to the internal organs. Thus, in a child that was attacked by foot and mouth disease after partaking of the uncooked milk of a sick cow, and upon whom an autopsy was held, Zürn saw numerous *aphthæ ulcera* upon the mucous membrane of the gastro-intestinal tract; and, in a child that had succumbed to foot and mouth disease, that had suffered particularly from marked diarrhea, Demme found discolored grayish, cuneiform foci in the liver, which invaded the structure deeply; an enlarged soft spleen; enlarged kidneys, the epithelium of the medullary substance showing fatty degeneration; swelling of the follicles of the intestine; and enlargement of the mesenteric glands.

DIAGNOSIS

The *diagnosis* of foot and mouth disease rarely gives rise to difficulties as soon as the characteristic changes upon the mucous membrane and the skin are observed in the patient and the history shows that the patient has had an opportunity of becoming infected with foot and mouth disease. If the clinical picture deviates from the typical course, which is by no means so rare, the diagnosis can only be made with certainty if the etiology of the affection is clear. The attempt must be made to obtain an accurate history, whether the patient has become infected in partaking of raw milk from sick animals or of their products, or if he has become infected in his occupation in handling sick cattle. Naturally, in this manner, only in a few cases, and then especially during the time of an epizootic of foot and mouth disease, can a thorough insight be had as to how the contagion has occurred. If this is not possible, then it becomes necessary to search for the etiologic factor. As, up to this time, we do not know the infectious agent of foot and mouth disease, nothing remains but to inoculate suitable animals with the contents of the vesicles or with the secretion of the ulcers in order to obtain certain knowledge regarding the disease. For this purpose, Bollinger advised utilizing goats or sheep. I desire, however, to call attention to the fact that if these animals

are used for inoculation purposes, a negative result of the experiment is not conclusive, that the disease is not due to the virus of foot and mouth disease, for Löffler and Frosch have observed in their experimental transmissions that sheep and goats are not very susceptible to inoculation, and among smaller animals only the calf reacts readily. For this reason, it is more advisable to use a calf in inoculation for diagnostic purposes. If the cause of the affection is recognized, foot and mouth disease can readily be differentiated from other affections which show similar symptoms.

Above all, confusion with *stomatitis* is possible, naturally, less with the ulcerative form, for disease and decomposition of the gums and mucous membranes does not occur in foot and mouth disease, in general, and is present in the case of *aphthous stomatitis*, which occurs particularly in younger children, due to other causes, at the time of dentition, and on account of affection of the digestive organs, appearing rarely in adults, particularly then in women during the menstrual period, during pregnancy or in the puerperium, showing itself upon the mucous membrane of the mouth or pharynx in the form of grayish-white deposits which may attain the size of a bean. These deposits are surrounded by a red areola, and adhere firmly to the mucous membrane, frequently changing into ulcers with raised borders and a lardaceous base. The mucous membrane and its surroundings is more or less markedly inflamed. As has been stated, in foot and mouth disease quite similar eruptions may appear on the mucous membrane of the mouth and pharynx, and Ebstein as well as Stierlin inclined to the view that aphthous stomatitis may possibly also be caused by the virus of foot and mouth disease.

The *acute exanthemata* must be considered in the differential diagnosis. Thus, in *varicella* vesicles appear upon the skin, and the similarity of this affection to foot and mouth disease may become greater by the fact that occasionally the appearance of vesicles upon the tongue has been observed in this affection. Foot and mouth disease may be confused with *measles* and *scarlatina*, especially at their onset, for at the start measly and scarlatina-like eruptions appear, these often accompanying the eruptions upon the mucous membrane or preceding them. A confusion with measles may all the more readily occur as the measly exanthem, as is taught by a case observed by Ebstein, may be accompanied by conjunctivitis and laryngitis. The further course of the disease clears the situation, often this may only be accomplished by the etiology.

That foot and mouth disease may show some similarity to *diphtheria* is shown by a case described by Ebstein, in which, besides constitutional symptoms and an erythema on the left arm, an ulcer resembling diphtheria appeared, which, however, did not contain diphtheria bacilli. In such an instance only the determination of the source of the infection may show the nature of the disease.

THERAPY

As in the other zoonoses, the best *prophylaxis* in man consists in the prevention of the distribution of the disease among animals, for with this the dissemination of the disease among men also becomes rarer. In this connection, great expectations were combined with the discovery of Löffler and Frosch.

These investigators observed that a large number of cattle two to three weeks after recovery from foot and mouth disease were immune for a few months, that the intravenous injection of a mixture of lymph from the vesicles of animals affected by this disease and the blood of immune animals, which contains protective substances, is capable of immunizing animals, especially after the mixture has settled for a long time, and that this immunity toward foot and mouth disease, at least in cattle, is transmitted to their progeny.

Unfortunately, this protective inoculation has not maintained itself in practice, and, therefore, we must limit ourselves to carrying out those measures which are advised by laws for the prevention of distribution of foot and mouth disease.

Of these laws, I shall only emphasize those which prevent the distribution of the disease in man. The law prevents the delivery of uncooked milk of sick animals on account of its infectious properties, it also prohibits the sale of skimmed milk, cheese, buttermilk and cream, but, what is most remarkable, does not prohibit the use of butter, which, as well as the other products produced from infectious milk, is able to transmit the disease in man, as has also been shown by investigations. The law allows the sale of milk that has been boiled, such as has been brought to a temperature of 100° C., or has been heated for at least a quarter of an hour at 90° C. Nevertheless, it is advisable to prohibit the use of even boiled milk of sick animals, especially for the nourishment of children, for this milk, as I have mentioned, shows decided alterations in its composition.

As the transmission of foot and mouth disease may also take place from person to person, the law is of great importance prohibiting all whose occupation does not make it necessary from entering stalls, such as cattle merchants, butchers, etc., these not being allowed to come in contact with sick animals, and requiring that all persons in close proximity with affected animals only be allowed to leave the place after washing their shoes and cleansing their clothes. According to the observations that have been made, these measures will only be effective in preventing the transmission of the disease if the clothing is changed and thoroughly disinfected.

Everything that comes in contact with the secretions and excretions of the sick should be rendered harmless by long-continued boiling, and, if this is not possible, by the prolonged action of a 5 per cent. solution of carbolic acid, which is an effective disinfectant.

On account of the danger of infection, sick human beings must be isolated. The treatment is largely symptomatic. The mucous membrane is painted with a 4 per cent. to 10 per cent. boric acid solution or with a $\frac{1}{2}$ per cent. to 2 per cent. solution of silver nitrate, the ulcers are touched with a solid stick of nitrate of silver, and a 5 per cent. potassium chlorate solution is used as a gargle. Siegel and Boas give a 5 per cent. potassium chlorate solution internally with success, a tablespoonful 3 times daily. The cutaneous eruptions are covered with Lassar's paste, phenomena on the part of the gastro-intestinal canal are treated with calomel besides regulating the nutrition; for the diarrhea bismuth subnitrate, tannin derivatives and opiates are given. In severe changes of the mucous membrane of the mouth and pharynx, the patient should only have fluid nourishment.

ACTINOMYCOSIS

BY A. NICOLAIER, BERLIN

Actinomycosis, or *ray-fungus disease*, is an *infectious disease* due to a vegetable parasite, the *actinomyces* (*streptothrix actinomyces*), which occasionally appears in man but is much more frequent in animals, occurring sporadically, more rarely in epizootics, especially in cattle, being observed much less frequently in the pig, horse and sheep.

In my opinion, this affection *cannot be classed among the zoonoses* as is so frequently done, although it must be admitted that direct transmission of this disease must occur from animal to man, but, in spite of the relatively frequent appearance of actinomycosis in cattle, this is a great rarity. It is unquestionable according to the present state of our knowledge, that infection in man and in animals originates from one and the same source; this will be described immediately, but actinomycosis in man and in animals arises under very different phenomena.

In cattle, under the influence of the ray fungus extensive swellings develop, especially in the upper and lower jaws, and more or less coarse, tumor-like formations of varying size appear upon the soft parts of the face, in the pharynx, in the esophagus, in the larynx, further, also in other organs; these commonly partly soften, and upon section show a pus-like character of the actinomyces in these soft areas, usually with numerous pale yellow, gritty, masses. Frequently there is also a thickening and hardening of the tongue.

In man the condition is different. Tumor formation is extraordinarily rare, under the influence of the pathogenic agent a granulation tissue forms which shows great tendency to fatty or purulent decomposition, so that abscesses readily develop. If the abscesses perforate through the skin or into cavernous organs, fistulæ remain, which heal with great difficulty. These changes gradually spread from organ to organ. Sometimes the pathogenic agent may be carried by the circulation to the most remote organs. Thus, in actinomycosis of man, according to the implication of separate organs in the morbid process, the affection shows manifold symptoms.

In animals, especially *in cattle*, the affection has been known for a long time. Veterinarians designate the disease according to the most prominent symptoms, such as the changes in the jaw, the pharynx and the tongue, and also regarding the probable course, the following terms being used: Cancer of the jaw, sarcoma of the jaw, spina ventosa, wooden tongue, tuberculosis of the tongue, etc. The name "actinomycosis" was first given to the disease by Bollinger, in 1877, when this investigator discovered the ray-fungus as the true cause of this affection.

Davaine, in 1850, described the yellowish granules in the fungus, with its whey-like formation, but he did not identify it correctly. Only twenty-five

years later, Perroncito recognized them as vegetable structures but did not bring them into causal relation to the pathologic changes with which they were found.

We owe this knowledge, as has already been mentioned, to Bollinger, who accepted the name "actinomyces," ray-fungus, from the botanist Harz, this referring to the radiating arrangement of the fungus elements in the granules.

A short time after the discovery of Bollinger, the disease occurring in man was correctly recognized. Without question, the granules of actinomyces in man were observed by Langenbeck in 1845, then in 1853 by Robin and Laboulbène, and in 1857 by Lebert. They were also described by these authors; but none of them looked upon them as vegetable parasites. J. Israël first recognized this in finding them in two patients in whom pyemic symptoms appeared, but did not bring them into causal relation with the affection which he assumed to be a new mycosis, nor did he recognize that these fungi were identical with the actinomyces of Bollinger. Only a year later, by the investigation of Ponfick, was it determined with certainty that actinomycosis also occurs in man, and the identity of the pathogenic agent of this disease in animal and in man was made certain.

ETIOLOGY

Upon the basis of a large number of cases, we know to-day that actinomycosis occurs more frequently in man than was assumed in the period in which the disease first became recognized. It is true, actinomycosis occurs in man much less frequently than in animals and, it is also well known that the affection occurs in all parts of the world, in man as well as in animals.

Although no age can be said to be exempt from actinomycosis, its appearance in children is very much rarer. The main contingent for the disease is shown by those between twenty and forty years, men being much more frequently affected than women, and in the male sex, especially those who are strong and powerful are most frequently affected, the disease occurring most often among the population of the country. According to the investigations of Samter, trauma favors the development of actinomycosis, especially that form occurring in the lungs and in the abdomen.

Regarding the *pathogenic agent of actinomycosis*, the *actinomyces* or *ray-fungus*, we are in the possession of positive knowledge gained by many accurate investigations. We must place this fungus in the group of streptothrix and, according to Rossi-Doria, it is best designated as "*streptothrix actinomyces*." The fungus appears in man and in animals in the form of round bands in the diseased tissue, especially in the softened areas of the same, the previously mentioned actinomyces granules, which may be recognized by the naked eye. The size of these granules is subject to great variation, the smallest having a diameter of 0.15 mm., the largest of 0.75 mm.; their appearance varies greatly according to their age.

According to Boström, to whom we owe the investigation of the morphologic and biologic properties of the ray-fungus, the young granules are soft, gray and translucent, and, for this reason, cannot be recognized so readily; later their consistence increases more and more, they become opaque, grayish-white, then yellowish, and when they are quite old they are glistening and

show a yellowish-brown, greenish-yellow, sometimes even black color, and, finally, may calcify. Then they appear gray, irregular in shape and may have a rough surface. These calcified granules are mostly found in the cicatrices which form in the diseased tissue. The youngest gray granules consist of a mass of thin branching threads which stain readily. In the more compact of these grayish nodules, the threads show granular swelling which may be stained according to Gram's method, whereas the yellowish granules, which are particularly found in the softened areas of the changed tissue, contain in their centre, threads with cocci-like structures which stain readily, which Boström believes to be spores of the fungus; in the periphery, the somewhat bent, club-shaped structures that are so characteristic of actinomyces granules are found, these being glistening and rigid. Occasionally the granules, especially if they are older, consist only of these bulbous formations.

In staining these structures, gentian violet, followed by picro-carmin, are to be used. The bulbs then show a red, the threads a dark violet color. Staining is unnecessary in order to recognize the structure of these granules, unstained preparations are sufficient for investigation. The addition of diluted caustic potash to the granules facilitates the investigation decidedly as they are cleared by this.

The ray-fungus may be cultivated upon artificial media, such as blood serum, agar, alkaline bouillon, etc., flourishing best with the addition of air and a temperature of 36° C. It forms at first gray, later yellowish-red, colonies, consisting of a loosely branching thread-work, which after some weeks coalesces into a folded covering membrane containing air-vesicles and spores, which occasionally upon its lower surface may show threads, and here be of a reddish color. Blood-serum cultures, after a longer period, liquefy, and in old blood-serum cultures there are found besides threads and spores, especially in the deeper layers, large bulbous structures similar to those occurring in the actinomyces granules.

The attempt to inoculate with these pure cultures or with actinomycotic material taken from animal and man have been unsuccessful, in spite of the fact that different varieties of animals have been used, and the positive results obtained by Ponfick, Rotter and others have been very much questioned by Boström, so that the absolute proof of the transmissibility of actinomycosis to animals has not yet been accomplished.

I desire to call attention to the results obtained by J. Israël and M. Wolff regarding the etiology of actinomycosis. These investigators carried out their experiments in connection with two cases occurring in man, which in their course showed no deviation from other cases. In spite of this, however, the results obtained by their experiments differ greatly from those that have been obtained by other investigators. They found that the ray-fungus obtained from these cases developed anaerobically in cultures, and in its growth and microscopic appearance showed other conditions besides the pathogenic action upon intraperitoneal injection into guinea-pigs and rabbits. As these results have also been confirmed by other observers, we must assume that two different fungi belonging to the group of streptothrices are the infective agents in actinomycosis, and, according to the latest investigations, this does not even appear to exhaust the possible number.

I have already mentioned that *direct transmission of actinomycosis from animal to man* is exceptional, in spite of the fact that actinomycosis in animals, especially in cattle, is a comparatively frequent affection. The few cases of direct transmission from animal to man have been mostly observed in persons that were occupied in looking after sick animals. The conveyance of actinomycosis to man from the use of milk, as is assumed by Bollinger, has certainly not been proved, and the transmission of the disease by the use of meat of animals affected by actinomycosis must be doubted very much, for the disease affects particularly the musculature of the tongue, pharynx and esophagus in cattle, this altering these structures, especially the tongue, so much that they are rendered entirely unfit for use. Actinomycosis in other muscles is rarely noted in cattle, and the actinomycotic changes which occur somewhat more frequently in the muscles of the pig are probably produced by some other pathogenic factors than by the agency of the actinomyces. Besides, if meat changed by the action of actinomycosis is sufficiently cooked before being partaken of it is harmless, for the fungus, as we know with certainty from the investigations of Domec, is very susceptible to the action of heat, at temperatures of 75° C. it is destroyed after five minutes.

In what manner does infection with the ray-fungus usually occur in man? It is hardly questionable any longer that in man, similarly to the case of cattle, the greatest majority of cases are due to vegetable constituents, especially particles of grain, to which the fungus adheres. That plants are readily infected with these pathogenic agents is taught by the observation that the ray-fungus could be found upon barley, rye, and beans; in earth infected with actinomycosis cultures it could be determined microscopically as well as by culture. On the other hand, we also know that as the germs of these fungi are very resistant to dryness they may remain virulent for more than a year upon dried grain. That vegetable particles, especially grain, play an important rôle in the etiology of human actinomycosis is shown by a large number of cases, in which vegetable constituents were found in the diseased tissues, and frequently the fungus of actinomycosis has been recognized, not only upon their surface but in internal portions. The entrance of the fungus into the human body may result without the agency of vegetable elements, but this need not be assumed by any means for all cases in which vegetable particles are absent in the diseased tissue; for, apart from the fact that such vegetable constituents may be exceedingly small, and for this reason be overlooked, they may even in the course of time be completely resorbed by the tissue, as was shown by Boström.

That vegetable substances play a rôle as transmitters of the ray-fungus, is further shown in that actinomycosis frequently develops in persons that have a habit of chewing grain, or of taking kernels of corn, blades of straw, or particles of bark into their mouths. Probably in connection with this is the fact to which I have already called attention, that the affection occurs more frequently in the country, and, according to the statistical results collected by Boström, the onset of the disease, which about corresponds to the time of infection, in the greatest number of cases, occurs in the period from August to January, therefore, during a period when the grain is ripe and dry, and during the time in which persons have much opportunity, in handling the

grain, to become infected by the ray-fungi which adheres to it. Naturally, other foreign bodies also, provided they are accidentally contaminated with the fungus of actinomycosis, may give rise to the development of the disease, but this can only be exceptional.

In what manner the fungus enters the body cannot be determined with certainty in all cases; often by the time that the cases are observed, the lesions at the point of entrance of the virus are healed, but then the fungus has the property of wandering in the tissue, and thus the first symptoms may arise at some distance from the point of infection.

In the majority of cases, however, the point of entrance may be determined, and it has been shown that this occurs most frequently by way of the *digestive organs*, namely by the oral and pharyngeal cavities. The infection may occur in the manner that foreign bodies, particularly vegetables to which the fungus may adhere, enter the mucous membrane of the mouth and pharynx; or defects of the mucous membrane, as after the extraction of a tooth or inflammation of the mucous membrane, may favor the entrance of the pathogenic agent. In the etiology of actinomycosis, J. Israël and also Partsch have ascribed a great rôle to caries of the teeth. That such a connection exists, is favored by the observation that in persons that suffer from actinomycosis of the throat and jaw, carious teeth are a comparatively frequent finding. But this connection is not, as assumed by these investigators, a direct one, in the manner that the fungus of actinomycosis finds an especially favorable point of development in the carious teeth, and from this point enters the tissues. Moreover, we must assume with Boström, that the development of the ray-fungus in carious teeth has not been proved, that caries of the teeth is only a predisposing factor for the development of actinomycosis in so far as defective teeth are a frequent cause of injury to the mucous membrane, loosening the gums so that the entrance of the infectious agent is rendered easier.

Far more rarely does the infection take its point of entrance from the deeper parts of the digestive apparatus, from the stomach, from the rectum. The cecum with its neighboring parts is comparatively the most frequent point of invasion of the ray-fungus in this region. According to Illich, catarrhal processes and ulceration in the bowel are said to favor the development of actinomycosis. The infectious agent, apart from those cases in which actinomycosis of the mouth or the pharynx or of the lungs occurs, reaches the gastro-intestinal tract in which the fungus is swallowed and then develops further in the intestinal canals. That infection arises from the meat of sick animals, I have already mentioned as not likely; however, even here vegetable constituents may transmit the infection, and this is proved by those cases of abdominal actinomycosis in which particles of grain have been found in the vermiform process.

The fungus rarely finds its way into the human body by means of the *respiratory tract*, especially the lungs, in which probably in the most cases it is taken up with the inspired air. It may happen, occasionally, that infectious material from actinomycotic changes of the mouth and pharyngeal cavities is aspirated into the lungs. In one case J. Israël observed that infection by actinomycosis found its origin by means of the fragment of a tooth.

Rarely does infection with the ray-fungus occur by means of the *skin*, the *external auditory meatus*, the *middle ear* or the *tear ducts*.

PATHOLOGY

The *pathologico-anatomical changes* of actinomycosis in man deviate decidedly from those observed in animals, especially in cattle, for tumor-like formations, which appear particularly in animals, are only occasionally observed in man, in the tongue, and were seen once in the brain by Bollinger and by Birch-Hirschfeld in the kidney.

As a rule, in man, a flaccid granulation tissue, often consisting of giant cells, develops, that soon undergoes fatty and purulent decomposition, so that abscesses form which contain a pus-like, occasionally offensive mass, in which pyogenic bacteria are present, with the yellowish actinomyces granules. If these abscesses are near the skin or in organs containing cavities they rupture, leaving fistulæ which heal but slowly and for this reason, existing for a long time. Occasionally in the morbid tissue healing by the formation of scars is seen, but, in spite of this, the changes develop still further, going from organ to organ.

It may be noted that from the affected soft parts of the lower jaw, the bone of which is but very rarely primarily affected in the form of granulation tissue, as a rule, secondarily affected, then being rough and denuded of periosteum, the process reaches the throat and the neck, thence, following the vessels to the bones of the skull and to the meninges, it gives rise to pachymeningitis, inflammation of the dura mater and inflammation of the meninges, and still further extends to the brain, in which actinomycotic formations and abscesses appear.

On the other hand, the so-called prevertebral phlegmons along the vertebral column may arise, causing the vertebræ to become carious, showing cavities, and being filled with granulation tissue and actinomycosis granules. The surfaces of the articulations between the vertebræ and ribs often show supuration, this distributing itself from the posterior mediastinum to the pleura and to the lungs. In the lungs smaller and larger foci form, consisting of granulation tissue which soon changes into abscesses which contain the characteristic actinomyces granules. These abscesses may rupture into the bronchi, or if they are adjacent to the pleura, into the pleural cavity, and when the pleuræ are adherent even through the skin or through the diaphragm. Often neighboring abscesses communicate with each other by means of fistulous tracts. In the region of these abscesses, interstitial inflammation is found which may extend over wide areas, finally causing a shrinkage of the lung. The pleura is commonly affected. The pulmonary pleura is often adherent to the costal pleura or to the diaphragmatic pleura or to the pericardium, occasionally effusions occur in the pleura, which may be either serous, sero-hemorrhagic or purulent.

Besides disease of the lung, occasionally also changes in the pericardium are noted, more rarely in the heart itself. The pericardium sometimes shows fatty granulations, occasionally the leaves are adherent, in such cases actinomycotic foci occur in the heart muscle, which may proliferate into the cardiac cavities, and sometimes granulations are even noted upon the endocardium.

From the thoracic organs, the changes may extend to the retroperitoneal tissue, or into the peritoneal cavity, involving its organs. Not infrequently the actinomycotic changes in the peritoneum take their start in the digestive organs.

The pathologico-anatomical changes which frequently develop in the oral and pharyngeal cavities will be described in the symptomatology. Rarely are ulcerative processes found in the esophagus and stomach. More frequently there are changes in the intestinal canal, especially in the cecum and the neighboring coils of the intestine. As a rule, nodules which ulcerate are present in the mucous membrane, especially in the submucous tissue. These not infrequently extend to the muscularis, sometimes cicatrices are found which are due to healed ulcers. Chiari once found plaque-like deposits containing the minutest actinomyces granules upon the surface of the mucous membrane. Often adhesions of the affected intestinal coils with the abdominal wall or neighboring organs are noted. Intra- and retroperitoneal abscesses, which communicate with each other, or, by means of fistulæ, communicate with the intestine or the urinary bladder, are not infrequent. Often hard infiltrations appear in the abdominal wall, which may soften in different areas.

If rupture of actinomycotic foci occurs in veins, the germs reach the circulation, then present metastatic changes in the various organs which otherwise show primary affection. But rarely do the germs of the ray-fungus distribute themselves by the lymph channel, which is in connection with the fact, that disease of the lymph glands is almost entirely absent. On the other hand, the leukocytes appear to play a rôle in the transmission of the germs.

If the disease exists for a longer time, amyloid degeneration of the liver, the spleen, the kidneys, and the mucous membrane of the intestine is a frequent finding.

SYMPTOMATOLOGY

If it is reflected that in this affection the infective agent enters the human organism in various ways, and that the changes produced by it extend from organ to organ, it will be readily understood that the clinical picture of actinomycosis may vary greatly. An understanding of the clinical picture may be more readily attained if the classification of J. Israël is accepted, according to which the point of entrance of the germ allows us to differentiate, a *head, neck, thoracic* and *abdominal actinomycosis*.

Among these divisions, *head and neck actinomycosis* are the most frequent. According to the statistics of Illich, which include 421 cases, this form occurred in about 50 per cent. The phenomena in this variety, as also in the others, arise in about four weeks after the entrance of the infective agent, and only in rare instances does this form of the disease run an acute or a subacute course, showing itself by development of an inflammation in the lower jaw, with great pain and a decided rise in temperature, the inflammation even spreading to the region of the neck, upon the floor of the oral cavity, upon the tongue and into the pharynx, not only giving rise to difficulty

in speech, but also to severe disturbance in nutrition, and occasionally even producing decided dyspnea.

Inflammation soon produces suppuration, and the pus contains besides granules of actinomyces, also pyogenic organisms. This clinical picture corresponds in many respects with *angina Ludovici*, and unquestionably such acute or subacute cases of actinomycosis of the jaw and neck has been diagnosed as an *angina Ludovici*.

Apart from these cases, which are, however, rare, head and neck actinomycosis continually shows a *chronic course* which may even last for years.

In case the affection is not complicated with infection by pyogenic microorganisms, there is no marked pain, nor is the temperature decidedly raised, and the general condition of the patient is not particularly influenced.

The disease takes its point of origin, as a rule, from the soft parts covering the lower jaw. In the gums, preferably in the neighborhood of the lower jaw, the development of a very consistent tumor is noted at first, which is but very slightly susceptible to pressure, gradually enlarging more and more, extending to the floor of the oral cavity and also to the cheek. Softening is noted in different areas and often the cutaneous covering of the cheek is puffy. The granulation tissue which is not softened may change into connective tissue and thus recovery occur. The softened areas sooner or later empty their contents, consisting of purulent material containing actinomyces granules, either externally through the skin, or into the oral cavity, and it is frequently a very long time before these openings close again.

Very disagreeable complications may arise through the bone of the lower jaw being diseased, more rarely in the manner that tumors form upon it, usually a periostitis occurs, which frequently causes great pain to the patient. If these alterations are already capable of giving rise to difficulty in taking nourishment, this may become entirely impossible when the muscles of mastication are affected, and, besides, when the floor of the oral cavity and the tongue, which is occasionally primarily affected, show marked changes. Apart from disturbances in speech, difficulty in respiration may arise, increased by the fact that by distribution of the process to the neck and throat, great alterations may occur in the larynx, which may even have become implicated and affected the thyroid gland, so that compression of the larynx occurs.

From the cheek, or from the upper jaw, which is comparatively rarely the origin of the disease, the process may distribute itself to the temporal region, thence affecting the bones of the skull, and then the meninges, or the brain itself; on the other hand a downward spread of the affection may occur, gradually implicating the thoracic organs.

Much less rarely in actinomycosis of the jaw and the neck, will *actinomycosis of the respiratory apparatus and of the adjacent organs be observed*, in spite of the fact that an infection of the respiratory organs occurs not primarily, but, as I have already indicated, mostly secondarily by an implication of the changes from the neck and head, less frequently from the esophagus or from the abdominal cavity, in rare cases also from infection by means of the circulation. Among the 421 cases collected by Illich, there were only 58 cases of primary actinomycosis of the lungs.

Primary pulmonary actinomycosis usually begins with the symptoms of a bronchial catarrh. The patients cough, have more or less copious expectoration, and in this, occasionally, actinomycosis granules are found. Then the etiology of the affection is clear. That only the signs of a bronchitis may occur, besides fever, chills followed by sweat, during the entire course of the disease and may last for seven years, was noted by Canali in one case. As in this case there is no autopsy report, the possibility must be thought of that phenomena of consolidation must have occurred in the lungs, which must have escaped observation, being deeply situated and covered by tissue containing air.

For it is the rule that in pulmonary actinomycosis, after a longer or shorter time infiltrations develop in the pulmonary tissue, so that dulness upon percussion is noted, and diminished bronchial breathing and ringing râles upon auscultation, and after the consolidated tissue-areas are decomposed the signs of cavity-formation may be present. Upon the whole, the findings in pulmonary actinomycosis show great similarity to those in pulmonary tuberculosis, and although pulmonary actinomycosis most frequently first develops in the lower portions of the lung, this cannot be utilized as a differential point in the recognition of the disease, for observation teaches that not so infrequently actinomycosis may also find its point of origin in the apex of the lung. Also the two diseases show great similarity in other respects, in so far as night sweats occur and the fever which is moderately high, as a rule, may have an intermittent and remittent type. Sometimes chills are even noted.

But very rarely does pulmonary actinomycosis run a course resembling galloping consumption.

In the further course the patients complain of difficulty in respiration, they become weaker, the cough becomes more marked, and the expectoration which is increased in amount shows large amounts of pus which is occasionally admixed with blood. Larger amounts of blood are but rarely noted in the sputum. Sometimes the expectoration may be rusty as in the case of pneumonia, or resemble raspberry jelly; often actinomycosis granules may be found in it but elastic fibres are said to be constantly absent.

The pulmonary affection is usually accompanied by pleurisy, which appears with high fever, pain, and friction sounds, as a pleuritis sicca or may even run a course showing the signs of an exudative pleurisy, the exudate may be serous, hemorrhagic or purulent. The pleurisy commonly causes adhesions of the pleural layers, with the formation of callosities which, in connection with the process of shrinkage that develops in the lung, give rise to great deformity of the thorax. The adhesion of the pleural layers frequently causes the process to produce changes in the thoracic wall, infiltrations form which decompose and rupture externally through the skin, leaving fistulæ which may communicate with cavities in the lung.

According to v. Korányi, if the changes occur in the pericardium and in the heart, pericarditis develops frequently, producing adhesions and dyspnea, abnormal cardiac action, dilatation of the heart and general dropsy. If the process distributes itself to the cardiac cavities and the papillary muscles are affected, the signs of valvular disease are noted.

Occasionally the affection extends from the organs of the thoracic cavity to those of the abdomen.

If, by means of disturbance in continuity, or, by the formation of metastasis, which gives rise to the symptoms of chronic pyemia, severe injury to vital organs occurs, the lethal termination appears early, but the course of pulmonary actinomycosis may last for several years, the patient succumbing by exhaustion, which may occasionally also be due to amyloid degeneration of the liver, the spleen, the kidneys, and the intestines. Recovery in pulmonary actinomycosis is exceptional.

A very changeable picture is shown by actinomycosis of the abdominal organs, as the symptoms vary so greatly according to the localization and distribution of the process in the abdominal cavity. Abdominal actinomycosis as well as pulmonary actinomycosis occurs primarily by the entrance of the infectious agent into the digestive organs as well as secondarily, partly by metastasis, partly by distribution of the affection from the region of the neck and lower jaw into the vertebral column, into the retroperitoneal tissue, partly from the thoracic cavity. According to the statistics of Illich, abdominal actinomycosis occurs somewhat more frequently than pulmonary actinomycosis; he found it 89 times in 421 cases.

Heller and Bargum noted actinomycosis of the abdomen running a course resembling enteric fever; this is very rare. Usually symptoms on the part of the gastro-intestinal tract introduce the disease. The patients complain of pain in the abdomen, partly circumscribed, partly more diffused, and these pains may occasionally become very severe, sometimes vomiting occurs, more or less decided diarrhea being present, but the disease may also run its course with constipation. Some cases show the symptoms of acute and chronic peritonitis, often the peritonitis is circumscribed, and the formation of an exudate occurs. This condition is more common in the ileo-cecal region; more rarely are the signs of perinephritis, parametritis, periostitis, or periproctitis present. In the further course of the affection, there appear in the skin or in the deeper tissues beneath, mostly painless infiltrations differing in size, which also vary in their position, according to the localization of the affection in the abdominal cavity. In perityphlitis actinomycotica they are found in the ileo-cecal region, in perinephritis in the lumbar region, in a localization in the psoas muscle below Poupart's ligament, in periproctitis in the gluteal region.

These infiltrates may soften, may rupture through the skin, into the bladder or into the intestine. In the pus, actinomyces granules are found, and their recognition in the urine or in the feces may decide a questionable diagnosis.

In some cases the appearance of an acute peritonitis or a septic infection may bring about the lethal termination, however, the course of pulmonary actinomycosis is mostly chronic, the affection lasting for years. In general, death which occurs in the course of time is due to cachexia, which is produced by the amyloid degeneration of the organs of the abdominal cavity that assists in this process.

I must mention briefly that the actinomycotic changes in the brain, which are for the most part secondary, are partly the result of metastasis, partly

due to an implication from neighboring organs, producing symptoms which, as is readily understood, vary greatly according to their seat.

Still a few words regarding cutaneous actinomycosis; this is not so frequently noted in connection with actinomycosis of other organs, in which the alterations gradually develop further, invading the subcutaneous tissue, and thus reaching the skin. Here, at the onset, hard infiltrations develop which later soften in different areas, and in these softened areas, the skin appears bluish-red and puffy. These softened areas rupture after a longer or shorter period, leaving fistulæ, which only heal with the greatest difficulty.

While in most cases the connection of affections of the skin with those of other organs is still to be proven, there occur, especially in the skin of the face, particularly in the cheek, actinomycotic changes which appear to the observer at first as primary, because a connection with disease of other organs, especially of the mucous membrane of the mouth, can no longer be demonstrated. These cases have, therefore, been designated by Tilanus and Hochenegg as actinomycosis cutis faciei. However, if an accurate history is taken in these cases, and the course of the affection is learned, it will be noted that a direct infection on the part of the skin may be excluded, and that previous changes have existed in the mucous membrane of the mouth. It will be found that these changes in the skin are of a secondary nature. The actinomycotic changes have their point of origin in the mucous membrane of the mouth, especially developing in the layers beneath the skin, and at the time the case comes under observation a connection with the mucous membrane can no longer be determined.

Primary cutaneous actinomycosis is a very rare affection. Up to this time but 23 cases are known, and of these cases, 7 occurred in women and 16 in men. It shows for the most part a chronic course and at its onset may produce severe disturbance, with constitutional symptoms. Besides the infiltrations which very frequently have a phlegmonous character, and in which, besides the ray-fungus, pyogenic organisms are also active, ulcerative changes are found which cicatrize centrally and, peripherally, develop further. The affection may invade deeper tissues, granulations occurring in the muscles, the fascia, and the periosteum, this leading to necrosis of the bone. Occasionally actinomycosis of the skin appears in multiple nodules similar to the condition in lupus, in which the recognition of the granules of the ray-fungus is very difficult. In some cases both forms are combined.

In the prognosis, the localization and extent of the changes is determining, above all if important organs are not affected and only small areas implicated, and if the diseased portions can be treated surgically, a favorable course may be counted upon. For this reason, head and neck actinomycosis is comparatively often cured, and this healing may even occur spontaneously. Sometimes relapses are noted, but this is not frequent in the case of head and neck actinomycosis. The chances are much more unfavorable in actinomycosis of the abdominal organs; with proper treatment recovery has been observed upon numerous occasions; however, relapses occur and the mortality is decided. The most favorable cases are those in which actinomycosis distributes itself upon the abdominal wall.

In pulmonary actinomycosis the prognosis is very unfavorable, for, as

already mentioned, recovery is exceptional. The chances are just as slight in a localization of the disease in the brain as in those cases in which the clinical picture runs its course with cholemia.

In the diagnosis of actinomycosis, the demonstration of the characteristic granules, which upon microscopic investigation show the bulbous terminations, is determining. Although neck and jaw actinomycosis may be diagnosticated from the slow, usually painless, hard, not sharply defined infiltrations which soften in areas, as well as secondary actinomycosis, from the changes which it produces, an absolute differentiation from similar diseases, for example, from inflammatory processes arising from carious teeth, that is, from scrofuloderma, the finding of the infectious agent is, nevertheless, of importance. It must further be remembered that, according to the observation of Garten, chronic purulent processes may run a course simulating actinomycosis, and fungi may be found which belong to the group of streptothrix; as a result of this, the finding of bulbous granules is not in itself conclusive that we are dealing with an infection with actinomycosis, but the positive proof must be attained by means of cultures.

The determination of the etiological condition is important in the diagnosis of pulmonary actinomycosis. The disease is easiest recognized when the actinomycotic changes are distributed on the thoracic wall, infiltrations having appeared that have ruptured externally, the granules which consist of the fungus of actinomycosis being found in the secretion of the fistulæ. A microscopic investigation of the granules is necessary under all circumstances, for, according to Ssavtschenko, suppurations occur in the thoracic wall which run a course similar to actinomycosis in which granules are found, resembling actinomycosis in the pus, which, however, consist of bacilli.

If these complications are absent in pulmonary actinomycosis, the recognition is difficult, especially the differentiation from pulmonary tuberculosis, to which, as has already been mentioned, it has great similarity. The differentiation is scarcely possible on the basis of the clinical findings. In these cases, in the differential diagnosis, the etiology is decisive. If tubercle bacilli are absent from the sputum, and if, on the other hand, the characteristic ray-fungi granules are present, which are most readily detected if the sputum is spread out upon a dark surface, the diagnosis of actinomycosis is certain. For microscopic purposes it is advisable to clear the granules by adding some caustic potash.

Abdominal actinomycosis can only be diagnosticated with certainty after the actinomycotic foci in the bladder have ruptured and the actinomyces granules appear in the urine or feces, or in the pus which has formed in the infiltrations upon the abdominal coverings.

Generalized actinomycosis, which usually appears under the picture of pyemia, occasionally, according to v. Korányi, may present the symptoms of enteric fever, of glanders, and of acute tuberculosis. Only the etiology can ensure certainty.

In conclusion, regarding prophylaxis and therapy of actinomycosis, although it is rare that actinomycosis is conveyed from animal to man, it is

still advisable to call attention to the possibility of infection in all those who come in contact with sick animals, advising a careful disinfection of the hands, especially before meals, and thorough care of the mouth. As, further, carious teeth play a rôle in the etiology of actinomycosis, especially of the jaw and the throat, even though being only predisposing causes, it is advisable if carious teeth are present to have them filled or extracted. Then it will be necessary in the case of all who have the habit of taking grain or similar substances into the mouth and chewing it to advise them that vegetable particles are the carriers of actinomyces and to call attention to the danger of contagion from this habit.

There can be no doubt that the favorable results that have been obtained in the therapy of actinomycosis are due to surgical treatment, and, for this reason, wherever it can be done, this treatment should be employed as early as possible. This is not the place to go into details regarding the treatment of individual cases according to the localization and distribution of the process. I only wish to remark, that less important and superficial foci had better be extirpated. If hard infiltrations exist, it is advisable to soften them by poultices, then to incise the softened areas and to remove all of the diseased tissue with the scissors and a sharp spoon, to thoroughly disinfect the wounds, covering them with iodoform, and to treat them openly. Fistulous passages are to be opened, iodoform gauze tampons used, or a 1 per cent. to 2 per cent. solution of corrosive sublimate employed. It has been variously advised to treat the wounds with a 10 per cent. carbolic acid solution or an 8 per cent. solution of zinc chlorid or to cauterize them with a solid stick of nitrate of silver or with a Paquelin cautery. In those cases in which an operative removal of the changed tissue is not possible it has been attempted to limit the distribution of the process by parenchymatous injections of anti-septic remedies, such as carbolic acid, tincture of iodine and a 1 per cent. solution of corrosive sublimate. The result, however, is very questionable.

Medical treatment of actinomycosis is subordinate to surgical. Among drugs, iodid of potassium deserves the greatest faith, and this valuable remedy could even be employed in those cases treated surgically. Whereas in some patients, even in large doses, no influence is noted on the actinomycotic process, there are still a number of cases and even severe ones in which the remedy has shown a decidedly favorable action, even having brought about cure. In the consideration of these cases, it must not be forgotten that cases of actinomycosis also heal spontaneously. Potassium iodid has no deleterious effect upon the infectious agent itself but it increases resorption of the diseased tissue, causing it to soften more rapidly, so that it prepares the tissue for surgical treatment. Of other remedies that have a favorable action in actinomycosis, I shall only mention arsenic.

In chronic cases, besides suitable nourishment, a stimulating treatment is indicated. In pulmonary actinomycosis the inhalation of disinfecting remedies, thus 1 per cent. to 2 per cent. carbolic acid, is to be tried.

IMMUNO-THERAPY

By JOSEPH McFARLAND, M.D.,

Professor of Pathology and Bacteriology in the Medico-Chirurgical
College, Philadelphia

IMMUNO-THERAPY is the practical application, for the prevention, amelioration, or cure of an infectious disease, of certain factors having to do with the cause, progress, or recovery of that disease.

It rests upon a substantial scientific basis, the principles of which have been gradually acquired during years of painstaking research in immunology. Like most branches of biological science, it had its beginnings in mystery and empiricism, and was foreshadowed in the attempts of the Chinese and other Oriental nations to prevent the destructive effects of smallpox.

The first experiments known to have been made in Europe began in 1718, when Lady Montagu, the wife of the British Ambassador to Constantinople, wrote an account of a method of ameliorating the effects of smallpox to friends in England, by whom it was popularized. Jenner developed a new line of thought and a new principle when he invented vaccination. Pasteur gave the subject an enormous impetus through his researches upon chicken cholera, anthrax, and rabies, and from his time immunology has become a more and more popular branch of physiological chemistry as it developed into a special branch of science in the hands of such men as Metchnikoff, Buchner, Nuttall, Behring, Kitasato, Weigert, Ehrlich, Roux, Haffkine, Wright, Wassermann, Calmette, Madsen, Flexner, and many others.

At the present time there is scarcely any department of medical science, and certainly no department of therapeutics, that rests upon so secure a scientific foundation as immuno-therapy, for its development has been accomplished through accurate work done in laboratories, and every successive step was not only a matter of actual demonstration, but was subjected to the most careful confirmation in laboratories in all parts of the world.

As the subject is essentially a technical one, and knowledge of it largely the possession of physiological chemists and other laboratory workers, it becomes a matter of importance that the elements of the science shall be explained before the practical applications thus far possible shall be considered.

The subject is an outgrowth of bacteriology, and as bacteria are the causes of the greater number of infectious diseases, immuno-therapy seems to many to be a department of that subject, though it is far broader in its scope. At present its chief successes have to do with the bacterial diseases, but experiments show that the same principles prevail among the protozoan infections,

and there is little doubt that as our knowledge of these maladies becomes amplified, the benefits of immunological research will be found to be available in them.

Since in all future considerations of the subject both bacterial and protozoan microparasites are to be embraced, it may be well to follow the French custom and speak of the organisms as *microbes* and of their respective diseases as *microbian*.

It is now universally admitted that microbes are pathogenic or disease-producing by virtue of certain poisonous metabolic products. These vary greatly both in quality and quantity. Some, called *endotoxins*, are insoluble or feebly soluble, and are liberated from the respective organisms, in whose bodies they are formed, only at the time of their death and dissolution. Others, *exotoxins*, are freely soluble and are as freely liberated by the organism during the entire period of their activity.

These toxic products, embracing what have been variously described by different authors as toxins, toxalbumins, and bacterioproteins, are all of proteid nature. Their physiological effects vary greatly among themselves, but they all have in common, and together with practically all heterologous proteid substances, the property of stimulating certain antagonistic physiologico-chemical reactions on the part of higher organisms, and hence are included in a group of miscellaneous character to which the name *antigen* has in recent years been applied.

By antigen, therefore, is meant any substance capable of stimulating an antagonistic reaction when introduced into the body of one of the higher organisms. The nature of the reaction is in itself unimportant so long as its tendency is antagonistic to the antigen.

As is known to the most cursory reader, immunity may be natural or acquired. In the present writing natural immunity finds little place, because the naturally immune animal does not become infected, is not susceptible to the stimulating effects of the antigen, and manifests no reaction, while the naturally susceptible animal, behaving in an exactly opposite manner, must either succumb to the infection or recover from it after a series of reactions attended with profound physiologico-chemical changes affecting the very constitution itself.

The first explanations of immunity were based upon these very constitutional transformations, and though they have become of historic interest only, were perhaps not so far from the truth.

The first hypothesis, that of Pasteur, is known as the "*Exhaustion theory*," and supposes that the infectious microorganisms during their sojourn in the body use up (exhaust) some essential substance the loss of which is incompatible with continued or future activity in that body.

This was quickly followed by the second hypothesis, or "*Retention theory*," of Chauveau, who taught that it was the saturation of the body with the waste products of the bacterial metabolism that rendered it an unfit medium for their future activities. Of the two theories, that of Chauveau comes a little nearer the truth as we know it now.

Both hypotheses passed into oblivion, however, with the appearance of the observations of Metchnikoff upon *Phagocytosis*, and the growing opinion that

the destruction of bacteria in the body and consequent recovery from infectious disease depended upon the facility with which the phagocytic cells seized upon and destroyed them. The comparative studies of Metchnikoff, and the broad biological horizon from which his deductions were made, were so convincing that many still cling to phagocytosis as the chief mechanism by which defence against infection is achieved.

Buchner, Nuttall, and others soon appeared, however, with an observation that shook the foundations of phagocytosis and divided the opinions of laboratory workers for many years. They observed that the blood plasma, blood serum, and other body juices possessed the power of destroying bacteria independently of any activity of the body cells. This idea was so incompatible with the fundamental tenets of phagocytosis, that they rejected Metchnikoff's idea that the body was defended by the phagocytes, and believed that the sole function of those cells was to scavenge the tissues and remove such microorganisms as had already been killed by the body juices. The controversies that arose from this opinion are most entertaining, and much labor, time, and effort were expended by the exponents of the two doctrines in endeavoring to refute one another. Buchner and his disciples attributed the destruction of the microorganisms to an enzymic substance—*alexin*—diffused through the body juices, and refused to attribute any important rôle to the phagocytes; Metchnikoff and his followers insisted that the enzyme was a cellular product normally contained within the phagocytes, giving them their bacteria-destroying power, and conferring this power upon the body juices only when through their destruction—*phagolysis*—the enzymic substance was liberated.

Throughout the controversy Metchnikoff and his adherents seemed to have the best of the argument, for many paradoxes of the "humeral theory" were incapable of satisfactory explanation. For example, the peculiar fact that when anthrax bacilli were introduced into the body of a rabbit, where they ought to be subjected to the destructive influence of the body juices in their greatest intensity, they usually multiplied with great rapidity and caused the death of the animal, though when the same organisms were introduced into rabbits' blood in a test-tube, they commonly died. No satisfactory explanation of this arose from the studies of the humeralists, though Metchnikoff explained it by supposing that the phagocytes were quickly destroyed during the coagulation and other blood changes imparting their enzymes to the serum.

Again, the humeralists were at a loss to explain how the bacteria which Metchnikoff inclosed in collodion capsules and placed in the body cavities of animals multiplied so successfully, though constantly subjected to the influence of the body juices.

During this period all the immunological experiments were directed toward the microorganisms as living entities and their chemical products ignored.

It became apparent through independent workers in the field that these products were of the utmost importance, and that the effects of bacteria were referable to them. Once this idea was grasped, the tide of experimental research changed, and it was found that natural immunity not only depended upon inability of microorganisms to invade the immune animal, but also upon the insusceptibility of the immune animal to the toxic products of the micro-

organism concerned. Gradually this idea was expanded to embrace immunological investigations upon other toxic and active substances than were of bacterial origin. Great impetus in this direction arose from immunization experiments with the bacterio-toxins. It was now remembered that Chauveau had referred immunity to retained bacterial products. Salmon and Smith found that when animals were repeatedly injected with filtered cultures of the hog cholera bacillus they were subsequently able to resist infection with that organism. Charrin found it possible to immunize rabbits against the *Bacillus pyocyaneus* by a preliminary treatment with filtered cultures of that organism; Bonome to do the same with the filtered cultures of *Bacillus proteus*, *Bacillus cholera gallinarum*, and the pneumococcus; Roux and Chamberland, and Roux individually were able to immunize animals against malignant edema by treating them with boiled cultures of the bacillus of malignant edema.

In all of these cases the immunity acquired by the experiment animals was comparable to that observed by the pioneer in immunological research, Pasteur, in his immunization of fowls against cholera by inoculations of attenuated cultures, and of sheep and other mammals against anthrax by his successive inoculations of cultures of increasing virulence.

The new discovery bore directly upon the doctrine of phagocytosis, but Metchnikoff remained immovable and saw no other explanation necessary than a change in the enzymic character of the body juices occasioned by the enormous phagolysis resulting from each toxin administration. This phagolysis with enzyme liberation conferred bactericidal and toxicidal powers upon the blood and tissue juices and so effected the defence of the animal.

Investigation of the bactericidal and toxicidal effects of these body juices led to some interesting observations. Thus Babes and Lepp found that when blood serum from animals immunized against rabies was introduced into other animals they acquired an unusual resistance to rabies. Ogata and Jasuhara found that the blood serum of animals successfully immunized against anthrax afforded protection against infection with the anthrax bacillus when injected into other animals.

The most significant contribution, however, came from Behring and Kitasato, who found that the blood serums of animals immunized against the toxins of diphtheria and tetanus bacilli, when mixed with cultures of the respective organisms, neutralized the toxins and destroyed their power to produce disease. Kitasato found that when mice were infected with tetanus bacilli, their lives could be saved by the intra-abdominal injection of serum from an animal immunized to tetanus, even if the injection was delayed until symptoms of the disease appeared. Behring, however, deserves the greatest credit, for he not only observed that the serum from the animal immunized against diphtheria toxin would prevent and cure diphtheria infection in the lower animals, but with great sagacity saw in this a method of treating diphtheria in human beings, and at once set about its practical application and popularization, thus conferring a boon upon humanity only second to that of the Jennerian vaccination of a century before.

It was clear that the antigen, in these cases the toxins of diphtheria and tetanus respectively, occasioned a reaction in the experiment animals (goat,

Behring; horse, Roux) that resulted in the formation of a substance, appearing in the blood serums of these animals, by which the toxic effects of the cultures and the filtered cultures (toxin) were neutralized, this neutralization taking place either in a test-tube prior to the introduction of a mixture of the two into an animal, or in the body of an animal into which they were separately injected, or in the body of a patient suffering from the disease into which the serum was injected for purposes of treatment. The interaction was immediate and direct and appeared to be of chemical nature, though not entirely understood.

The new observation appeared incompatible with phagocytosis, for it was admitted that the phagocytes did not visibly participate in the reactions. Metchnikoff, however, declined to yield, and with diminished force maintained that the toxin-antitoxin reaction resulted from the toxin-destroying function of the enzymic substances resulting from the exaggerated phagolysis in the blood of the animal furnishing the antitoxic serum during the course of the treatment known as immunization.

The hasty and erroneous conclusion was reached by many that all forms of infection would prove amenable to treatment by means of immune or antitoxic serums, and experiments were conducted in all laboratories with disappointing results. Of these experiments, however, some were of great interest as amplifying the known facts and permitting a more intelligent appreciation of the nature of the reaction. Thus, Ehrlich discovered that such antitoxic serums were not formed through microbic antigens alone, but through the stimulation of other antigens as well, and was able, by immunizing animals to ricin, a toxalbumin derived from the castor-oil bean, abrin, a toxalbumin of the calabar bean, and robin, a toxalbumin from the bark of the locust tree, to secure antiricin, antiabrin, and antirobin respectively. Calmette also found that the toxalbumin in cobra venom behaved as an antigen and stimulated the formation of an antibody (antivenene) by which the poisonous effect of the cobra venom was destroyed both *in vitro* and in the animal body.

It soon became evident that antitoxins arose solely through the stimulating effects of powerful soluble toxins—exotoxins—and that where such were absent no such substance arose during the treatment known as immunization or the progressive administration of increasing doses of bacterial products. If during immunization of animals to nontoxic or feebly toxic bacterial cultures any reaction products arose, they were of different quality and of different action. This was further confirmed by the fact that their administration upon the general plan of the antitoxic serums not only resulted in no benefit to the patient, but in some cases did him harm.

There were also certain paradoxes in the behavior of the serums that could not be explained, among which "Pfeiffer's phenomenon" attracted wide attention. This was an effect of the immune cholera serum upon the cholera spirilla that took place as follows: Guinea pigs are susceptible to intraperitoneal infection with virulent cultures of *Spirillum cholerae asiatica*, and suffer from peritonitis characterized by exudation and an enormous increase in the number of the introduced organisms. They are also easily immunized by a few preliminary injections with avirulent cultures. Now, when a healthy

guinea-pig is injected with a virulent culture of cholera spirilla and then, shortly after, with some serum from an immunized guinea-pig, no infection follows, and when from time to time drops of fluid are withdrawn from the abdominal cavity and examined, the organisms, instead of multiplying, are observed to gather together in clusters, become inactive, and shortly undergo a granular disintegration. How this came about appeared to be inexplicable, since no similar destruction of the organisms was effected when the microorganisms and the immune serum were mixed together *in vitro*.

Here knowledge rested for a time, until new light was thrown on the whole subject through Ehrlich's investigation of the constitution of the diphtheria toxin and the formulation of his *Lateral Chain Theory of Immunity* and the investigations it stimulated.

In the available amount of space that can be devoted to the subject it is as impossible as it might be unprofitable to enter upon the steps that led to the formulation of this theory, so that it will be treated briefly and discussed only in so far as it enables an intelligent comprehension of the problems embraced by the subject Immuno-therapy.

The studies of the diphtheria toxin brought Ehrlich to the conclusion that it consisted of molecules characterized by qualities which he described as *haptophorous*, or combining (from the Greek, *ἅπτω*, to seize hold of), and *toxophorous*. Its effects upon the body cells depend upon the ability of the haptophores to attach themselves to the cells, which they are able to do only when the cells are provided with hypothetical combining adaptations to which he gave the name *receptors*. The visualization of this union is illustrated thus:

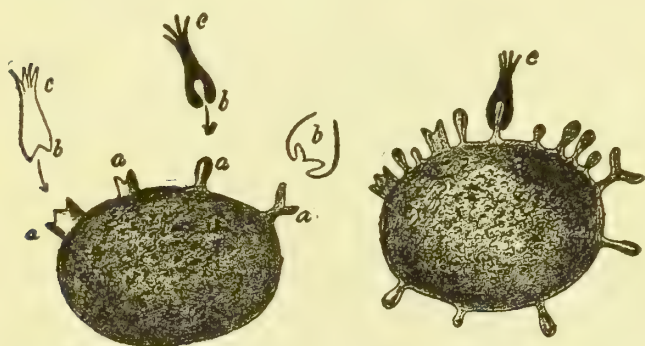


FIG. 61.—DIAGRAMMATIC REPRESENTATION OF A CELL WITH VARIOUS RECEPTORS (a) AND SOME TOXIN MOLECULES (bc) WITH HAPTOPHOROUS GROUP (b) AND TOXOPHOROUS GROUP (c) ONE OF WHICH HAS ATTACHED ITSELF TO THE CELL. (Ehrlich.)



FIG. 62.—REPRESENTATION OF COMBINED HAPTOPHORE AND TOXOPHORE ADAPTATIONS. (Ehrlich.)

In this diagram it is seen that though receptors having the appropriate affinity and adaptation for the fixation of the haptophores are present, no opportunity is afforded for the influence of the toxophore except when such a combination as is shown in Fig. 62 can be effected, when the cell can be poisoned.

It seems probable that the similarity exists between the haptophores of certain of the toxins and nutrient molecules commonly fixed by the cells.

If we now pause a moment to consider this much of the theory, it will be found that natural immunity can be referred to the absence of those receptors by which the toxophorous elements are enabled to combine with the cell. But it is not solely by virtue of toxophorous influences that the cells may be injured, for it can be conceived that should all of those receptors, by virtue of which the cell nutrition is carried on, be preëmpted by the haptophores of the foreign proteid, the cell would suffer retrogressive change and might be destroyed should no means be provided for meeting such a contingency.

Weigert amplified Ehrlich's idea by suggesting that when the cell is so encumbered and its receptors thus rendered inutile, a regeneration of receptors was effected. Working upon this hypothesis, it might be inferred that should an animal be given increasing, frequently repeated doses of any foreign proteid by which its receptors were occupied in increasing numbers with each increase of the dose, the receptor regeneration effected might ultimately reach such a point that in the interim the cell would be encumbered with them and the time would arise when they would be thrown off into the surrounding juices and perhaps carried to the blood. This idea is suggested in Fig. 64.

But the diagram shows a possibility that is of the utmost importance, i. e., that the receptors cast off by the cell, retaining their primitive combining affinity, are capable of meeting the haptophores in the blood and uniting with them, thus saving the cells from the embarrassment of their union.

In the presence of these free receptors in the blood and body juices of the immunized animal Ehrlich sees the explanation of the antitoxic power of the blood and of the toxin-destroying power of the serum as it is seen *in vitro*.

This reaction of toxin and antitoxin is immediate and direct, and can only obtain in those cases in which soluble exotoxin is found by the microbe.

In those cases in which the microbe forms only endotoxin that is liberated at the moment of its dissolution, no such reaction is possible. A different explanation must therefore be sought, and Ehrlich and Morgenroth found it

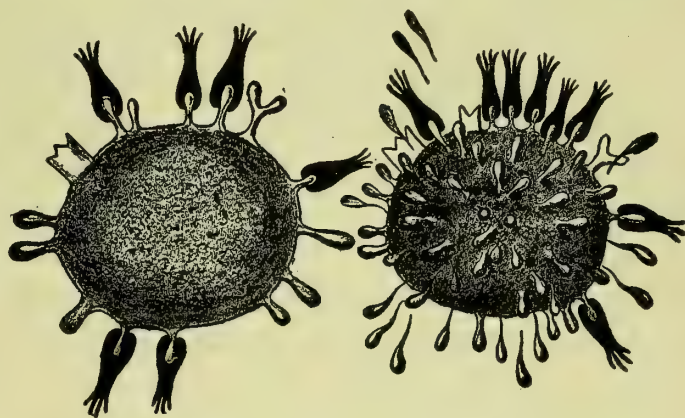


FIG. 63.—FIGURE ILLUSTRATING WEIGERT'S THEORY OF THE REGENERATION OF RECEPTORS. (Ehrlich.)



FIG. 64.—REPRESENTATION OF THE LIBERATION OF THE EXCESSIVE RECEPTORS FROM THE CELL AND THEIR COMBINATION WITH THE HAPTOPHORES OF THE TOXIN. (Ehrlich.)

in their studies of the mechanism of hemolysis, which formed the starting-point of all intelligent understanding of the bacteriolytic and cytolytic functions.

These observers found that the mechanism of hemolysis by hemolytic serums—that is, the serum of an animal that had been subjected to a succession of doses of heterologous blood corpuscles—was indirect in nature and accomplished through the coöperation of two essential factors. One of these has become universally known as the *complement*, and is present in normal blood. The other is known as *amboceptor*, and is an immune product, varying from a trace found in normal blood to much in bloods from immunized animals. The complement appears to be a nonspecific enzymic substance capable of dissolving animal and vegetable protoplasm. The amboceptor is a specific substance resulting from the stimulating effect of some antigen. The mechanism leading to hemolysis is illustrated below (Fig. 65).

A glance at this diagram shows that it is impossible for the complement to attach itself to the corpuscle except in the presence of the amboceptor.

The first question that arises is the natural source of the amboceptor, seeing that it is something that can be increased in quantity through experimental manipulation of animals, and this is answered by supposing that



FIG. 65.—SCHEME ILLUSTRATING THE MECHANISM OF HEMOLYSIS. (Ehrlich.)

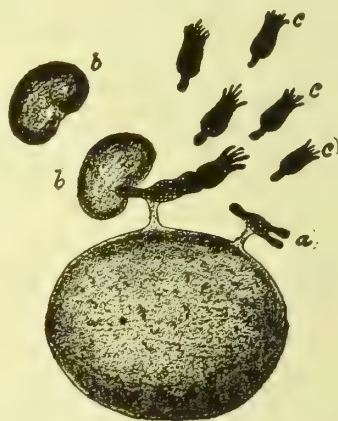


FIG. 66.—REPRESENTATION OF A CELL UPON WHOSE SURFACE ARE SEVERAL RECEPTORS OF THE SECOND ORDER. (Ehrlich.)

it is a special kind of receptor through which the indirect cellular activities are conducted, for it must be remembered that in normal physiology many indirect transformations are known, as, for example, that of proteids by pepsin in the presence of hydrochloric acid, that of proteids by trypsin in the presence of enterokinase, the solidification of fibrin factors by the ferment in the presence of calcium salts, and the coagulation of caseinogen by rennet in the presence of a calcium salt. It therefore seems not unreasonable to suppose that some of the cell functions are enzymic in nature and are carried on by virtue of some unknown kind of intermediary to which the name amboceptor is applied. In fact, the nature of the intermediary is partially known, for it is found that certain processes analogous to those under consideration are accomplished through the intermediation of certain lipoids, of which one, lecithin, is known, since the work of Keyes, to activate the hemolytic activity of cobra venom.

Ehrlich visualizes this intermediate cell action as accomplished through a special type of receptor by which the useful molecule is caught and brought into contact with the enzyme upon which it is acted so that the cell may derive the profit of the transformation products (Fig. 66).

An antigen of such effect that its stimulation would lead to the formation of many such amboceptors might eventually lead to their free occurrence in the blood and so impart to the blood serum the property of fixing the available complement to the antigen and thus destroying it.

It is most important to observe that, in the reactions following the experimental treatment of the animals furnishing serums whose activity is manifested by a specific solvent action founded upon such a combination as is indicated above, it is the amboceptor alone that increases. The source of the complement is unknown—presumably it is derived from the leukocytes—and no means have been discovered for materially increasing it.

When we come to apply these facts regarding the indirect or intermediate reaction of immunity to the explanation of the general facts of immunity, we at once become able to explain many things not otherwise clear, as will be shown below.

Before passing to a brief consideration of the forms of immunity it is, however, of some importance to see that Metchnikoff remains unmoved by the additions to knowledge made by Ehrlich, and declares that with certain reservations they are simply amplifications of his own ideas. He does not agree with Ehrlich that the body cells generally participate in the formation of the antitoxins, amboceptors, and other immune products, but stands squarely upon his previously formulated belief that the whole matter is referable to the phagocytes whose energies are carried on by virtue of two enzymic substances—he has added one—*macrocytase*, which is a sensibilizing substance (*substance sensibilisatrice*) or a fixing substance (*fixateur*) by which the bacteria or other microbes are prepared either for actual phagocytosis, or for destruction by the other enzyme, *microcytase*, which is the complement.

In a writing the purpose of which is to lead up to the therapeutic application of immune products rather than to delve into the mysteries of immunity as a physiologico-chemical condition, it is unnecessary to enter upon a consideration of the specific precipitins, the agglutinins, the aggressins, etc.

There is, however, one more factor that must not be overlooked, the nature of which is obscure, but which is unquestionably deserving of attention in all cases of active immunity in which phagocytosis is important. It was discovered by Wright, and is called *opsonin*. It is supposed to be of such a nature that its action upon microbes so modifies them as to make them more easily susceptible to phagocytosis. The opsonins are not substances used for treatment, but factors toward the production of which treatment is directed, and a quantitative estimation of which enables the physician to appreciate the good or bad effects the patient experiences from bacterio-vaccination.

The following scheme displays the present state of knowledge regarding immuno-therapy, its purposes and possibilities:

IMMUNO-THERAPY

I. PROPHYLAXIS.

1. IMMUNITY INDUCED BEFORE EXPOSURE TO INFECTION.

A. ACTIVE IMMUNITY.

- a. *By inducing a mild attack of the disease by the use of a carefully selected virus.* } INOCULATION { Variola
Yellow Fever
- b. *By the employment of a much-modified virus* } VACCINATION (Jenner) { Variola
- VACCINATION (Microbination) (Pasteur) { Chicken Cholera
Anthrax
Quarter Evil
Cholera
Plague
Typhoid

B. PASSIVE IMMUNITY.

- 1. *By Injection of Antitoxic Serum*—ANTITOXINATION { Diphtheria
Tetanus

2. IMMUNITY INDUCED AFTER EXPOSURE TO INFECTION AND DURING THE INCUBATION PERIOD OF THE DISEASE.

- 1. *By the employment of comminuted tissue containing the essential cause of the disease in an attenuated form.* } MICROBINATION Rabies

II. TREATMENT.

1. BY PRODUCING ACTIVE IMMUNITY.

A. *By aiding the Bacteria-destroying Mechanism.*

- a. *By employing killed or modified cultures to excite phagocytosis through increase of opsonins, etc.* } MICROBINATION { Acne, Furuncle
Carbuncle
Chronic Suppuration
Chronic Gonorrhœa
Typhoid
Malta Fever
Tuberculosis

B. *By Aiding the Toxin-enduring Powers.*

- a. *By stimulating antibody formation during the course of a prolonged infection.* } TOXINATION { Tuberculosts
Lepra

2. BY PRODUCING PASSIVE IMMUNITY.

- A. *By injecting antitoxic serums to neutralize toxins produced in the course of the infections.* } ANTITOXINATION { Diphtheria, Tetanus,
Snake Bite, Hay
Fever, Plague, Tuberculosis, Lepra
- B. *By injecting antimicrobial serum to aid in the destruction of the microbes through the action of the specific amboceptors.* } ANTIMICROBINATION { Cerebro-spinal Fever,
Gonorrhœa, Plague,
Dysentery, Pneumonia, Erysipelas,
Scarlet Fever, Puerperal Fever, Typhoid,
Anthrax, Tuberculosis

In reviewing this tabulation a number of facts of interest present themselves.

The first to which attention may be called is that the facts apply with equal force to both man and the lower animals, so that they are real biological principles. A second is that much has been learned by parallel studies of diseases of man and the lower animals. A third, that the same affection may be attacked through the application of any one of several principles. Thus, taking typhoid as an example, it is possibly subject to prevention through vaccination, may possibly be ameliorated by the judicious administration of modified cultures during the course of the disease, or may possibly be subject to improvement through the introduction of specific immune serum containing bacteriolytic amboceptors. Again, gonorrhea in its inactive stages may be benefited by bacterination, or may be cured in its rheumatic form by the administration of antigonococcic serum.

Using the table as a guide, the consideration of the measures it embraces will be next examined in some detail and in reference to the particular diseases to which they have been applied.

I. PROPHYLAXIS

1. INDUCED BEFORE EXPOSURE

a. BY MITIGATION WITH A CAREFULLY CHOSEN VIRUS

VARIOLATION—*Variola*; *Yellow Fever*

Variola.—The Chinese and other Oriental nations have from time immemorial been in the habit of inducing smallpox by artificial means. Whether they did so upon superstitious, religious, or scientific bases has not been determined, and probably deserves little attention, since the methods were uncertain in action and in effect. The Turks, however, had greatly advanced in the technic, and it is worth while to inquire what they did. The most interesting account is to be found in the letters of Lady Mary Wortley Montagu. This method may with doubtful propriety be included in this writing, yet it is an endeavor to prevent death from smallpox by choosing the time and form of smallpox. It seems rational that the healthy child inoculated with virus from a mild case, may escape the dangers resulting from the exposure of a feeble child to a virulent case. The results seemed to justify the means, and the method introduced into England continued to be practiced there until the demonstrations of Jenner showed the superiority of vaccination. The chief objection to the method was that the disease induced in no way differed from that which was to be prevented except in severity; each inoculated individual was a source of contagion from which an epidemic might arise. The severity of the induced malady could not be controlled and many died from the inoculation, who might have lived longer before being overtaken by accidental infection. Still, for a long time it appeared to be worth the risk, and was eagerly practiced so long as there was nothing better.

Yellow Fever.—Shortly after the discovery of the rôle of the mosquito in the transmission of yellow fever by Reed, Carroll, Lazear, and Agramonte, the

thought occurred to Guiteras that prophylaxis against the disease might be accomplished by experimental inoculation. By carefully choosing mild cases of the disease, by permitting laboratory-bred mosquitoes to bite them, and then by permitting these infected mosquitoes to bite healthy nonimmunes, Guiteras conceived it possible to control the conditions of infection by controlling the number of mosquito bites, and so induce a mild attack of the disease, which would, of course, be followed by immunity. When the method was put to trial, however, the occurrence of several deaths showed that it was too dangerous to be continued.

b. BY THE EMPLOYMENT OF A MUCH-MODIFIED VIRUS

VACCINATION	}	JENNERIAN— <i>Variola</i> .
OR		
MICROBINATION	}	PASTEURIAN— <i>Chicken Cholera, Anthrax, Rabies, Quarter Evil, Cholera, Typhoid, Plague, Tuberculosis</i> .

Jennerian Vaccination

It is difficult for one whose life has been spent among civilized peoples of the present day and enjoyed the luxuries and safety of modern conditions and institutions, to translate himself in thought to a period a century or two anterior to his own time and contrast the conditions then existing with the present. It is difficult to hark back in imagination to a period not so very remote, when the great city of London was without paved streets, when there were no sewers or drains; when the rain water mired the streets and remained in puddles during clear weather; when hogs wallowed in the puddles and ate the garbage thrown into the streets for the purpose; when lady's maids emptied chamber slops from upper windows into the same streets sometimes to the discomfort of pedestrians happening to be below; when men wore boots and ladies clogs in fair weather, and were carried in chairs because it was impossible to walk, and when the obstacles in the streets were such that the chair men not infrequently stumbled and fell, precipitating "my lady" into the street; when the streets were not lighted at night and it was unsafe to go out after dark except with a goodly escort, and street brawls were of hourly occurrence; when the water came from wells only, many of which being polluted, continually spread illnesses of various kinds; when epidemics of plague, cholera, smallpox, and other now preventable diseases raged in periodical epidemics; when no isolation of the ill was practiced, and when everybody had had, had, or expected to have smallpox, which was endemic; when unmarked faces were at a premium, and when pitted and seamed faces and sightless eyes resulting from smallpox were on every hand.

Frightful times, yet such as existed in all great cities a few centuries ago!

When the foul fiend, smallpox, thus lived with mankind, tormenting, disfiguring, and destroying him, many of the lower animals suffered from diseases peculiar to the times, bearing a partial resemblance to variola, becoming more and more rare as variola was held in check, and now rarely seen. Of these, only vaccinia need be mentioned, because it alone became of subsequent

interest. Probably, like the others, it would have been largely forgotten had it not been for certain peculiarities in its transmission to human beings. The lesions of this disease were usually to be found upon the cow's udder and teats and consisted of a localized inflammation during which vesicles, and then pustules, made their appearance, to be followed by rather extensive crusts. It was communicable to those who handled the parts—dairy maids, etc.—and affected their hands, causing a like local disturbance with the formation of vesicles, pustules, and crusts. One attack was followed by subsequent immunity. But this was not all; those not having had smallpox before were most frequently affected, and having suffered from an attack of the vaccinia, or cowpox, were found not to take smallpox thereafter. This was common knowledge among the lower classes for generations before Jenner's time, and upon several occasions led thoughtful persons to experiment upon the verity of the matter. Thus, in 1791, Nicholas Plett, a schoolmaster of Starkendorf, in Germany, having considered the subject, experimentally infected three of his pupils with cowpox, and found that they did not subsequently take smallpox. What other unrecorded experiments may have been made cannot be determined, but the public and professional minds were interested in "inoculation" as suggested by Lady Montagu, and interest in other means of preventing smallpox declined.

One investigator, however, was brought into the field in a peculiar manner. Edward Jenner, a physician of skill and training, meeting a pretty milkmaid with smooth complexion, and contrasting her beauty with the scarred faces about her, inquired how she had escaped smallpox for so long a time. "I cannot take smallpox, because I have had cowpox," she replied. This led Jenner to thinking and later to experimenting. The first experiment was made in 1796 upon a lad who was to receive the usual "inoculation." Before this was done, Jenner infected him with cowpox, permitted the disease to run its course, and then performed the variolous inoculation, but without result. It seemed clear that the vaccinia (cowpox) had prevented the variola (smallpox). This was the beginning of that great system of prophylactic immunotherapy against smallpox, to which Jenner applied the term *vaccination*, from *vacca*, a cow. It took many years to effect its popularization, but at the present time the whole world is reaping its benefits and smallpox remains a comparatively rare and easily controlled disease.

The genesis of the vaccine virus is a matter of speculation, but scientific men are pretty much in accord in believing that the variolous and vaccinal viruses have had a common origin, and that vaccinia is but variola modified through the differing physiologico-chemical conditions the virus encounters in the tissues of the cow. What these conditions are is unknown, but enough experimental work has been performed to indicate that through a proper sequence of animal transplantations, the virus loses its variolous qualities and comes to assume the vaccinal character. This alteration of behavior is thoroughly consistent with the known facts of immunity and is paralleled with many observations upon the specific causes of other diseases, as will be shown below. The transformation in the quality of the virus in the cow is of fundamental importance to the success of the immunization effected. The variolous virus induces a severe *contagious* constitutional affection with a *general-*

ized eruption; the vaccinal virus, a mild and *noncontagious* constitutional affection with a *localized eruption*.

The advantages of vaccination over variolation are thus self-evident and need no further amplification.

The source from which the virus is to be secured is a matter over which our forefathers waged long and bitter battles. To many persons it was repugnant to think of infecting themselves or others with virus taken from a lower animal, and to them the virus, if it was to be used, must be taken from a human being. It is unnecessary to dwell upon the respective merits other than to point out why nearly the whole world eventually reached a unanimity of opinion in favor of virus of bovine origin. It is a fundamental fact that, other things being equal, infections are more easily transferred from animal to animal of the same kind, than to animals of other kinds, and that many infections peculiar to animals of one species are not transferable to those of another. When the virus is transferred from arm to arm, other bacterial infections in man may be transplanted, and another disease thus simultaneously transmitted. Experience showed that this method in the hands of the ignorant, the careless, or the inexperienced sometimes resulted in the transmission of syphilis, erysipelas, and other peculiarly human maladies. Of the diseases of cattle scarcely any, and none of any importance in this relation, can be transferred to man, hence the bovine virus is *comparatively safe*. It has been argued, especially by Mexican authorities, that the human virus affords a more prolonged immunity than the bovine, but exact figures are lacking to confirm this. Even should it be a fact, however, it would be preferable to repeat the vaccinations than to use the less safe human virus.

In a recent paper before the American Public Health Association, Huddleston discussed virus prepared by inoculating rabbits, but though for many reasons these animals might be preferred to the bovines, the method is so limited in applicability as to be of doubtful expediency.

The preparation of the vaccine virus would be a matter of great simplicity were it not for the rigid cleanliness that must be practiced, and for the difficulty of maintaining uniformity in the potency of the product.

In brief, the preparation of bovine vaccine is as follows: According to the preference of the operator, calves or heifers may be chosen. They are first placed in a receiving stable, where they are subjected to a variety of tests to prove their healthy condition, and are fed upon special food (sterilized milk for calves). After being thoroughly washed and their hoofs scrubbed, they are removed to the operating room, where the entire thorax, abdomen, thighs, and nates are shaved, disinfected, and the disinfectant washed off with warm solutions. Linear scarifications are next made through the epiderm, care being taken that no blood is drawn, after which the virus is applied and rubbed into all the scarifications. The animal is next transferred to a special stable, where it stands upon a clean wooden rack, its head in stanchions, where it remains under careful observation and conditions of rigid cleanliness until the lesions mature and the virus (called pulp) is ready to remove. The animal is then removed once more to the operating room, the shaved surface now covered with the cloudy vesicles thoroughly washed, a disinfecting solution applied and carefully washed off with sterile water, the surface dried with

sterile towels, and the "pulp" removed from the vesicles with a medium-sharp curette. After this the animal is slaughtered, or may be kept until it recovers. Great difference of opinion at one time prevailed as to the particular product that was to be employed for vaccinating the human subject and the particular means of applying it. Some threw away the "pulp" and used the serum that subsequently exuded, drying it upon ivory points with which the vaccination was to be performed. Time and experiment have shown the best methods, and at present the "pulp," mixed with a certain bulk of glycerine, is ground between glass rollers until it is reduced to a state of fair uniformity, after which it is sealed in glass tubes and stored away for a time, during which the glycerine slowly kills such microorganisms as it contains.

There is no doubt but that in the past the manufacture of vaccine virus was conducted under conditions that would make one shudder at present, but ignorance was responsible for them, and at present the surgical clinic is not more clean and orderly than a vaccine virus manufactory, nor is it conducted with greater attention to scientific principles. Moreover, all such establishments are conducted under government licenses, are subject to inspection, and may be closed by the withdrawal of the license if conditions are not favorable.

Besides the essential microbe of vaccinia the virus always contains numbers of skin cocci. These are harmless organisms, but it would be better if they could be excluded. No means of doing so is available at present, as their disappearance is invariably accompanied by loss of the potency of the product.

To be certain of the absence of all accidentally entering injurious bacteria, much care is taken. In all laboratories every lot of virus is examined bacterioscopically and bacteriologically, and in all instances inoculations into animals are first practiced to make sure that tetanus and like organisms are not present.

Various objections to vaccination are urged by those ignorant of the conditions. Thus, a few persons seem to possess natural immunity against vaccinia and so cannot be vaccinated. It does not of necessity follow that they may not be susceptible to smallpox. A few persons are so susceptible to vaccinia that the eruption does not remain localized, but distributes over the surface of the body (generalized vaccinia) and may resemble smallpox. Vaccination in rare cases leaves little immunity, and the individual can be revaccinated with success at frequent intervals. Such individuals not acquiring much protection against vaccinia may not acquire immunity against variola. Others can be successfully vaccinated, remain thereafter immune against vaccinia, yet prove susceptible to variola. All of these aberrations from the normal are extremely rare, but commonly form the stock in trade of those opposed to the method.

Again, many confuse the *operation* with the *effect*, and suppose that because one has undergone the operation of vaccination he must have experienced the effect. This is a fruitful source of error. The operation is performed for the purpose of producing but one effect—the disease, vaccinia. To have been scratched upon the arm, to have had a sore arm, signifies nothing unless the specific lesions developed. To be vaccinated without the desired effect constitutes *inefficient* vaccination; with the desired effect *efficient vac-*

cination. Any vaccination that does not confer immunity against variola for a number of years is *inefficient vaccination*.

Like all acquired immunity, that which results from vaccination is not of indefinite duration, but persists only so long as the physiologico-chemical effects produced in the body continue. It is therefore necessary to repeat the operation several times during life.

The accidents of vaccination are so unimportant in comparison with the good accomplished that small attention need be paid to them except to impress upon all the importance of care in the preparation, use of the virus, and the subsequent care of the subject vaccinated. The accidents have sometimes depended upon microörganisms accidentally present in the virus; more frequently upon their subsequent introduction into the sore.

Pasteurian Vaccination

Chicken Cholera.—In the course of his early experiments with microbes Pasteur met with a surprise that opened an entirely new field for experimental investigation: Some cultures of the bacillus of chicken cholera having been neglected, it became necessary to work them over again, and in the course of the experiments they were inoculated into some fowls. To the vexation of the operator the birds did not die, so the cultures were shown to have lost their virulence and to have become useless. New cultures from fresh cases of chicken cholera were obtained and proved to be highly virulent, killing the fowls in the usual length of time; but when these new virulent cultures were inoculated into the fowls that had formerly received the nonvirulent cultures, the fowls survived. Here was an observation of much interest and importance—when animals are inoculated with attenuated or harmless cultures of a microbe, they may acquire immunity against infection with virulent cultures of the same microbe. The outcome of this experiment was the foundation of the greater part of Pasteur's experimental work in immunity. The first application was naturally in chicken cholera, when it was found that a single injection of an attenuated culture afforded the fowls subsequent immunity against the disease. The method has been and is still used with satisfaction where chicken cholera abounds.

Anthrax.—Receiving his clue from the spontaneous attenuation of the cultures of the chicken cholera bacillus, Pasteur next set about determining whether it might be possible to effect an artificial attenuation of cultures in which the spontaneous change was slow or absent. Experimenting with the anthrax bacillus, a large spore-bearing organism, the cause of splenic fever in animals, he found it possible to cripple the bacillus by heat, by germicides, and by other unfavorable conditions. Putting the results of experiment into practical application, he found that when sheep were treated (1) with a culture whose spore-bearing power had been destroyed and whose virulence was attenuated by cultivation at an elevated temperature until it might kill mice but not guinea pigs, (2) with a culture that killed mice and guinea pigs, but only occasionally rabbits, they became sufficiently immune to withstand the effects of inoculation with virulent cultures from an animal recently dead of the disease.

It was almost as difficult for Pasteur to convince the world of the practicality and efficiency of this method as it was for Jenner with regard to vaccination, but in a public demonstration, held at Pouilly-le-Fort in 1881, he was so successful that his opponents ceased their clamor. Statistics from the French bureau, collected by Roger, show that by the employment of this method of vaccination the mortality among sheep has been reduced from 10 to 0.94 per cent, and among cattle from 5 to 0.34 per cent.

Quarter Evil.—The success of this method was followed by a similar method of vaccination or microbination for the control of quarter evil of cattle. Upon this subject Kitt and Arloing, Cornevin and Thomas worked with excellent results. They found that when muscular tissue containing the specific bacillus of this disease was pulverized and dried at a somewhat elevated temperature for several hours, the microbes became attenuated to such an extent that their inoculation was followed by a moderate local reaction only, and the animals given immunity. The method is extremely simple and inexpensive, and the statistics of Guillod and Simon, based upon 3,500 cases, show a death rate of 0.5 to 2 per cent, as contrasted with 5 to 20 per cent in unprotected animals.

The vaccine is now commercially prepared and is used very widely.

Cholera.—The first important application of the Pasteurian method in human medicine (apart from Pasteur's own experiments) was made, in 1892 by Haffkine, for the prevention of cholera. For this purpose two vaccines or cultures of different degrees of virulence are employed by hypodermic injection. The first is of such strength that it produces but a moderate local reaction. It, however, paves the way for the second, which is of such virulence that if administered without the protection afforded by the first injection, extensive tissue necrosis or death must inevitably result.

The effect of the double injection is an immunity of considerable duration that seems to be sufficient to prevent the occurrence of cholera in a majority of those so treated. The death rate among those inoculated has been found to be about one-half that of those not so treated. The method, therefore, is doubly serviceable; it diminishes the incidence about one-half and reduces the death rate among the inoculated about one-half.

Plague.—Applying the same principle, Haffkine experimented with cultures of the bacillus of bubonic plague and believed that good prophylactic results were obtained. The bacilli, as virulent as could be secured, were cultivated in bouillon, floating drops of oil being used to secure the "stalactite formation." After this growth has continued for a month or so, with frequent agitation of the culture so as to break up the already formed stalactites and permit the development of new ones, the whole culture is killed by exposure to 70° C. for an hour. Of this killed culture from 1 to 3 c.c. are injected beneath the skin. A mild febrile reaction, a local hyperemia, and some enlargement of the lymphatics follow, and the individual is rendered immune for a month or more. The greatest attention must be paid to the condition of the patient at the time of injection, for should it happen that he is already infected, the injection accelerates and intensifies the disease.

In the Summarized Report of the Plague Research Laboratory for 1902-4 statistics are given of 200,000 cases so immunized. These show that

but few of the immunized persons contracted the disease, and that those who did suffered from a less severe attack, the death rate being only about one-third of that seen in the unprotected.

The temporary duration of the immunity afforded by the Haffkine prophylactic led Kolle and Otto to experiment with living attenuated cultures. An antiplague serum was simultaneously injected into the experiment animal, and the effect of the living culture was found to be more lasting than of the killed culture. Kolle, and Strong endeavored to utilize attenuated living cultures for the active immunization of human beings. Strong, at Manila, was able to experiment upon condemned criminals, and found, by beginning with an injection of $\frac{1}{100}$ "öse" of attenuated plague culture into the first individual and gradually increasing the dose in one after another of a large number of persons, that a normal person could tolerate a whole agar culture of the bacillus without danger. He treated 42 persons with this large dose of living plague bacilli without injury, but with febrile and local reactions. The serums of these persons were highly agglutinative and also protected experiment animals against infection with the bacilli.

The Haffkine method is the only prophylactic against plague that is shown, through the lapse of time and by sufficient numerical and statistical evidence, to be useful.

Typhoid Fever.—Basing his ideas upon the Pasteurian method as practiced by Haffkine for the prevention of cholera and plague, A. E. Wright began in 1897 a series of experiments for the control of typhoid fever by means of a prophylactic culture injection. The "vaccine" consisted of 1 c.c. of a bouillon culture killed by heat. During the years 1899–1901 soldiers in the British Army in India, Egypt, and South Africa were thus treated, the total number amounting to about 100,000. The inoculations were not always made under conditions that were satisfactory as regards the exact laboratory control of the prophylactic, nevertheless, the results were very gratifying and quite comparable to those obtained in the application of the same method for the control of cholera and plague—viz., in those inoculated, the incidence was diminished about one-half, and of those diseased in spite of the prophylactic the mortality was reduced by one-half. Numerous papers upon the subject appear in the British Medical Journal, the Lancet, and in the Journal of the Royal Army Medical Corps between the years 1903–8. Most of these papers are kindly disposed toward the method.

Confirmatory results were obtained by the French, as shown in the communication of Nattan-Larvier¹ and by the Russians, as shown in the paper of Dzierzgowski,² though this experimenter prefers repeated to single injections, and thinks better results are obtained by the employment of subtoxic cultures.

It should be said for the Wright method that among the enormous number of cases upon which it was practiced there never was a death or a permanent ill effect.

The Germans began a thorough investigation of the subject in 1905, papers by Gaffky, Kolle, Hetsch, and Kutscher appearing in the *Klinische Jahr-*

¹ Presse méd., 1904, No. 8.

² Sitzungsbericht der mikrobiologische Gesellschaft zu St. Petersburg, 1904, Mai 31.

bücher, Bd. xiv, 1905, and papers by Mushold, Steudel, Hetsch and Kutscher, Flemming, Morgenroth, Echardt, Eggert and Kuhn in the *Veröffentlichungen aus dem Gebiete des Sanitätswesens*; herausgegeben von der Med. Abtheilung des Kgl. Preus. Kriegsministerium, 1905, Heft 28,¹ by Kolle,² and by Kutscher.³ These contributions include the investigation of the changes induced by the inoculations as shown by increase in the agglutinative and bacteriolytic character of the serum, etc. They also discuss the respective merits of living and killed cultures in bouillon (Wright) and agar, as contrasted with Shiga's "free receptors" formed by permitting the bacilli to undergo spontaneous autolysis, and the "inoculation powder," a dry preparation suggested by Wassermann. Such statistics as they were able to gather from a somewhat limited number of cases confirm Wright's conclusions.

The method is not to be recommended except when an epidemic is in progress or is threatened. The studies of the blood show that after the injection a "negative phase" occurs—i. e., a period of diminished resisting power, during which susceptibility is increased, hence the inoculated must be carefully watched and prevented from contact with sources of infection for a short time until the physiological equilibrium is once more established.

Tuberculosis.—The control of bovine tuberculosis by means of a prophylactic vaccination was first recommended by McFadyen in 1901.⁴ Shortly after, it was undertaken upon a great scale in Germany by Behring,⁵ whose experiments are still under way, and in this country was begun extensively under the auspices of the Pennsylvania State Live Stock Sanitary Board by Pearson and Gilliland.⁶ These experiments are still in progress, but the occasional reports show gratifying success, and it is hoped that when the final reports are received they will fulfill the expectations of those interested.

The method consists in primary injections of highly attenuated bacilli, followed by subsequent injections of cultures of greater virulence.

No prophylaxis of tuberculosis among human beings, based upon this general plan, has been suggested, and such means of prevention scarcely seem to be desirable.

2. INDUCED AFTER EXPOSURE TO INFECTION AND DURING THE INCUBATION OF THE DISEASE

By the Injection of Comminuted Tissue Containing the Essential Cause (Microbe) of the Disease in a Modified Form—Rabies

Rabies.—It is in the prevention of this disease by microbination during its long period of incubation that Pasteur achieved undying fame.

Rabies being a rare affection caused by the implantation of a specific virus by the teeth or claws of rabid animals, there is no necessity for prophylactic

¹ Aug. Hirschwald, Berlin.

² Deutsche med. Wochenschrift, 1905, No. 12.

³ Med. Klinik, 1905, No. 21.

⁴ Jour. of Comp. Path. and Therap., June, 1901.

⁵ Beiträge zur Experimentellen Therapie, 1902, Heft 5.

⁶ Jour. of Comp. Med. and Vet. Archives, November, 1902; Univ. of Pa. Med. Bull., April, 1905.

treatment except when exposure to infection that may prove to be rabid has actually occurred. Were it not for the fortunately prolonged incubation period of the disease, no means of treatment known to medical science would be of the slightest avail. But the incubation period averages about six weeks, and sometimes extends over many months, during which time there are no symptoms, and the virus is finding its way to the central nervous system, where its final localization leads to an explosion of convulsive seizures terminating in death. Reflecting upon this long incubation period, Pasteur surmised that it might be possible to effect immunization so that the microbe would be destroyed en route to its final destination and the disease prevented. The difficulty was that the virus itself was of an unknown nature, and even up to the present time it remains of doubtful nature, for it is uncertain whether the bodies of Negri are parasitic microbes or not, and it is impossible to experiment with them apart from the tissue in which they are contained.

Acting upon his experiences with the virus of chicken cholera, Pasteur found that the virus of rabies was subject to attenuation, and that this diminution of virulence, which took place spontaneously with the passage of time, could be experimentally effected with accuracy under the exact conditions of laboratory research. After many trials he located the most pure and most appropriate virus in the central nervous system—that in the saliva was always hopelessly contaminated—and after a prolonged series of trials succeeded in devising a system of drying the tissue over calcium chloride for purposes of attenuation. After many efforts and the expenditure of infinite pains he was able to transform the variable “street virus”—i. e., infectious matter from a dog dead of hydrophobia—into a “fixed virus,” no longer variable, and modifiable to suit the conditions of his experiments. Some who oppose the method upon unintelligent comprehension of its details lose sight of this primary and fundamental step. By prolonged cultivation in rabbits and subjection to uniform conditions, the virus was “fixed” or rendered constant in action under given conditions.

The material for immunization best fitted for practical application was found to be the spinal cord of a rabbit. The method by which it is secured is as follows: The standard virus is introduced into a rabbit, which, after the lapse of a given time, becomes paralyzed and shows the typical symptoms of the disease. The animal is then killed with chloroform or by a blow upon the head, is skinned, the body carefully disinfected and protected and the spinal cord removed under conditions of rigid asepsis. The spinal cord is at once transferred to a sterile bottle, in which it is suspended over some calcium chloride placed in the bottom for the purpose of absorbing the water. Here the cord remains, slowly drying, for a varying number of days, and the longer it remains and the more it dries the less virulent the contained microorganisms become. Every well-equipped laboratory for the purpose of treating dog-bites, etc., has on hand at all times a large number of such cords of various ages ready to be prepared for use.

The treatment consists in the injection of one after the other of a series of viruses, beginning with those too mild to effect injury and gradually ascending to those of some virulence.

The material for injection consists of a thorough emulsion of a portion

of the appropriate spinal cord in sterile salt solution, forming a bulk of about 2 c.c. The injections are made into the subcutaneous tissue and cause some pain and local irritation that soon disappears as the tissue remnants are absorbed.

The first injection usually consists of a spinal cord that has been dried for about ten days; the second is given the next day from a cord dried about the same length of time. Every day an injection is made, each being prepared from a spinal cord that has not dried so long, and hence contains microbes of greater virulence than those that were used before.

The exact details of treatment and preparation vary with different institutes, but the practical application usually extends over three to four weeks, with daily injections in the beginning and alternate days toward the end, the final dose usually consisting of about 2 grams of spinal cord dried for only three days.

Although Pasteur devised the treatment in 1889,¹ not much improvement has been made upon his methods.

The treatment is now available either gratuitously or at small expense in many municipal and state laboratories. The laboratory of the New York Board of Health, New York, even prepares the spinal-cord emulsions, packs them in ice, and ships them to a reasonable distance at very small expense, so that the treatment can be administered by the family doctor.

II. TREATMENT

1. BY INDUCING ACTIVE IMMUNITY

A. BY STIMULATING THE BACTERIA-DESTROYING MECHANISM

a. By Employing Dead or Modified Cultures to Promote Phagocytosis through the Activity of Opsonins, etc.—BACTERINATION—*Acne, Furuncle, Carbuncle, Ulcer, Gleet, Pneumonia, Typhoid, Malta Fever, Tuberculosis.*

Before passing to the particular affections susceptible to benefit by this method of treatment it seems important that those intending to apply it shall be acquainted with the general principles upon which the method depends and shall understand the means by which the treatment can be controlled so that good and not ill to the patient shall result. It is unquestionably true that by the proper application of these "bacterio-vaccines" much good can be accomplished; it is equally true that their misapplication results in harm. The way having been blazed by others, many will be content to follow in their footsteps, but the careful man should endeavor to accomplish better work by the more thorough study of the effects his treatments produce.

Bacterination, or bacterio-vaccination, is a method of treating infectious diseases by means of modified cultures of the specific organisms of the particular infection concerned, based upon the knowledge that the injection of a proper number of the organisms at an appropriate time is followed by an increase in the phagocytic activity of the body cells toward those particular

¹ Compt. rendu de l'Acad. des Sciences, Paris, 1889, cviii, p. 1228.

organisms. At the same time an increase in the specific amboceptors may occur, so that a double benefit is conferred upon the patient, but the chief aim is toward increasing phagocytosis, and so destroying the infectious agents. It is because of the increase in cellular activity caused by the stimulation induced in the patient's own body that the reactions are called "active immunity."

In a sense the experiments with this form of treatment are quite old. Thus the Jennerian vaccination against smallpox, if performed after exposure to the disease and during the incubation period, may prevent the disease or mitigate the attack.

The Pasteurian vaccination against rabies may be considered to come in for its share of consideration, and is truly an active immunity, brought about, after infection, by microbination with the modified specific organisms.

An endeavor to apply the method to the treatment of tuberculosis was made by Koch in 1901.

The method received its real establishment as a therapeutic measure at the hands of Sir A. E. Wright in a series of important papers, beginning in 1902, and became an exact method with the publication by Wright and Douglas of their paper upon "Opsonins."¹

That phagocytosis varied in different conditions of immunity, appearing in immunized animals when absent in normal animals of the same kind, or becoming intensified in activity when resisting animals were further immunized, had been known since the days of the warfare between the phagocytologists and the humeralists, but no other explanation was offered than that the cells, "having once met the microbes and combated them, acquired a subsequent appetite for them."

Denys and Leclef² were the first to show that the cells were in some manner influenced in their phagocytic behavior by the serum or substances it contained. Their observations were confirmed by Mennes,³ but no application was made of the observations until later, as the demonstration of phagocytosis was difficult. Leishman⁴ devised an easy method of estimating phagocytosis by human white blood corpuscles, but still no practical use of the estimated phagocytic power of the blood in the treatment of the patient was made. But, in 1903, Wright and Douglas developed a new technic by which the study of phagocytosis was made easy, given a new impetus, and made an important adjunct to practical medicine.

These observers found that when human leucocytes (phagocytes) were washed and suspended in physiologic salt solution, their phagocytic activity varied with the addition of serums from different individuals. Thus Wright's leucocytes in Douglas' serum behaved differently from Wright's leucocytes in Wright's serum in their phagocytic activity. This observation led to much experimental investigation of the source of the variation and to the belief that phagocytosis is determined in part by the presence in the serums of certain substances, to which they applied the name "Opsonins," from the Latin

¹ Proc. Royal Soc., lxxii, p. 357.

² La Cellule, 1895, xi, p. 198.

³ Zeitschrift für Hygiene, etc., 1897, xxv, p. 413.

⁴ British Med. Journal, 1902, p. 73.

opsono, I cook, I prepare food for. By a study of the "Opsonic Index," which is determined by dividing the phagocytosis stimulated by the patients' serum by the phagocytosis of a normal serum, it is possible to draw certain valuable inferences regarding the state of the patient, and before the subject can be further pursued it becomes necessary to outline the technic of determination.

The Opsonic Index.—To make a test of the opsonic index it is necessary to be provided with certain simple apparatus and materials:

- A uniform suspension of bacteria,
- A suspension of washed leucocytes in physiologic salt solution,
- The serum to be tested,
- A normal serum for comparison.

The Bacterial Suspension.—The same bacterial suspension can be employed for a variety of purposes—testing agglutinative power of the blood, testing the opsonic index, testing the bactericidal power of the blood, and for administration as a bacterio-vaccine.

The culture to be employed is best grown upon agar-agar for twelve to twenty-four hours, young cultures being easier to separate than older ones. The bacterial mass is taken up by means of a platinum loop, transferred to a tube of physiologic salt solution and rubbed gently upon the glass just above the fluid, the tube being tilted from time to time so as to bring the fluid to the culture mass, moisten it, and carry away the loosened organisms. What remains is again rubbed and the tilting again repeated, and so on until a uniform suspension is secured. If the culture is difficult to separate, as in the case of tubercle bacilli, it may be rubbed up with the salt solution, which is added drop by drop in a small agate mortar or rubbed between glasses.

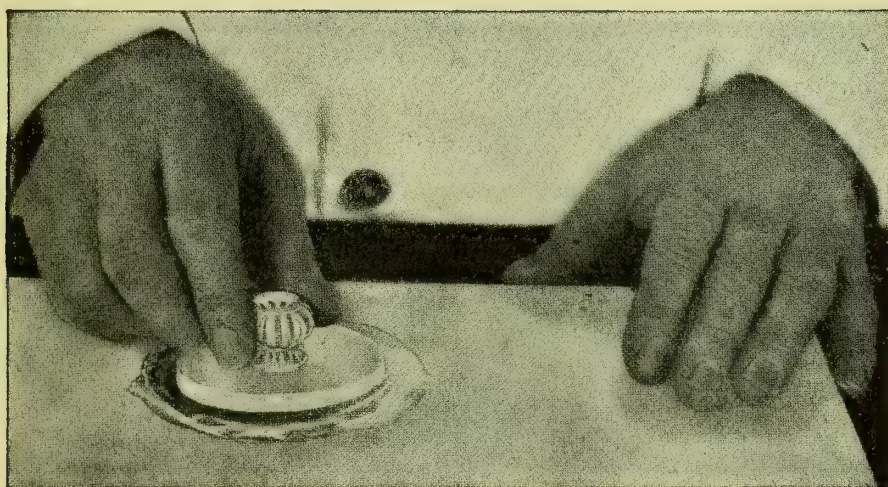


FIG. 67.—METHOD OF RUBBING THE BACTERIA WITH SALT SOLUTION TO MAKE THE SUSPENSION. (Miller.)

If the suspension is to be of tubercle bacilli a twelve- to twenty-four-hour culture is, of course, impossible, and some of the pellicle from the surface of bouillon or from a glycerine agar tube may be employed. The suspension should impart a very slight opalescence to the fluid. In accurate work the number of bacteria in a given quantity of the suspension should be uniform, and to accomplish this Wright counts the bacteria and by dilution standardizes his preparation. His method of standardization by counting is very ingenious

and consists in mixing one volume of the suspension with an equal volume of normal blood and three volumes of physiologic salt solution. After thoroughly mixing, a smear is made upon a glass slide, stained with methylene-blue and eosin, and, with the aid of a diaphragm fitted to the eye-pieces, he counts both red corpuscles and bacteria in many successive squares until two hundred corpuscles have been counted. It is then a

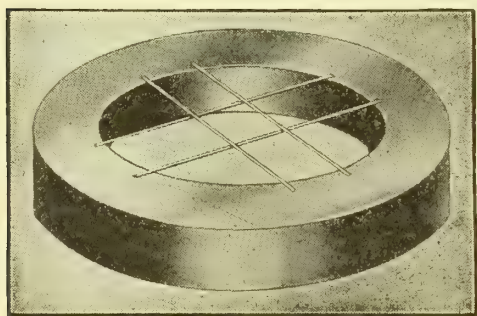


FIG. 68.—DIAPHRAGM OF EYE-PIECE SHOWING HAIRS IN POSITION. (Miller.)

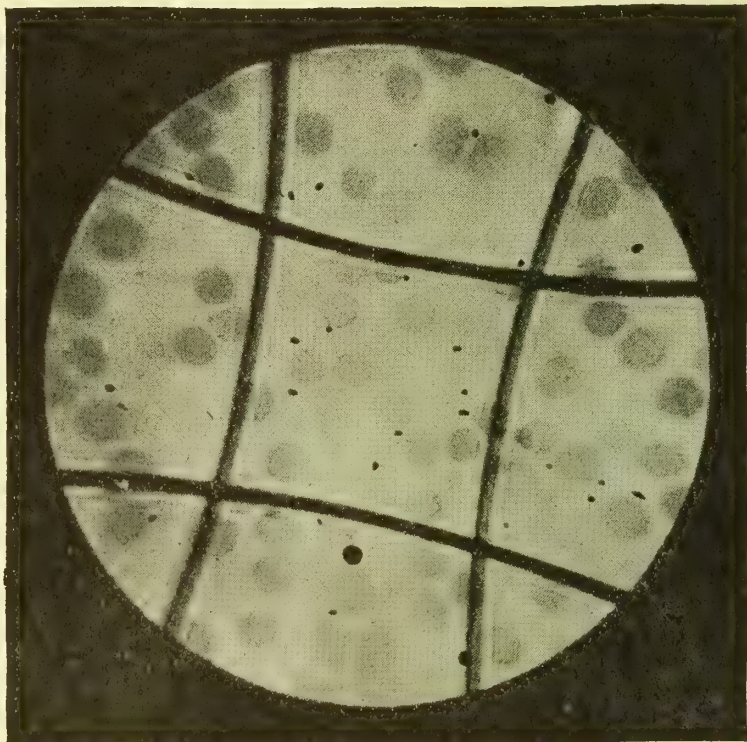


FIG. 69.—PHOTOMICROGRAPH SHOWING CROSS-HAIRS IN THE EYE-PIECE AND RED BLOOD CORPUSCLES. (Miller.)

matter of simple arithmetic to determine the proportion of bacteria to corpuscle, remembering that there are 5,000,000 corpuscles per c.mm. of normal blood.

The exact number of bacteria appropriate for making the opsonic index calculation is a matter of personal opinion with the operator, but after having made various trials to determine with what concentration the counting is most satisfactorily accomplished, pains should be taken to make use of similarly dense suspensions in all the accurate work.

The counting method finds its most important application where the suspension is to be used for purposes of bacterination, for it can then be told exactly how many bacteria were given the patient in each cubic centimeter of the preparation.

The Suspension of Washed Leucocytes and the Serums.—The washed leucocytes need not be free from admixture with erythrocytes, but must be free from serum, and must be obtained in large numbers. The

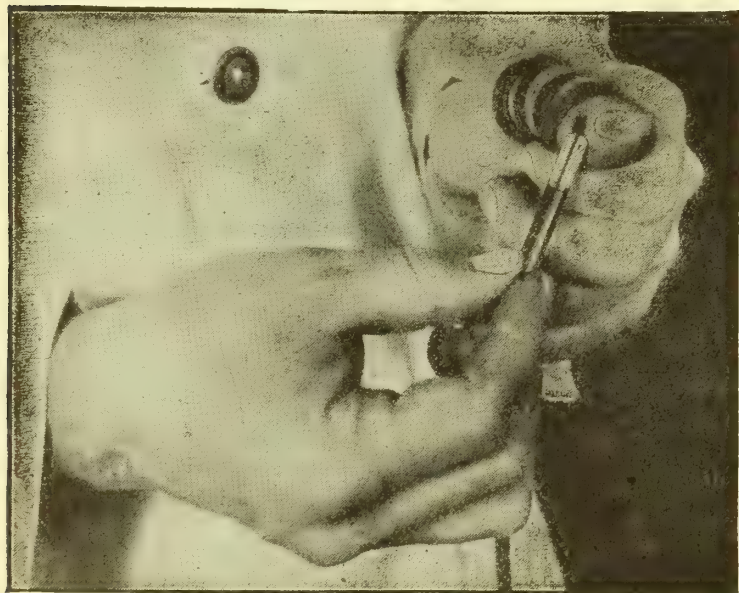


FIG. 70.—COLLECTING BLOOD FOR CORPUSCLES. (Miller.)

leucocytes should come from the patient whose serum is to be tested, rather than from a normal individual, since the test is really intended to determine the variation in the behavior of the leucocytes brought about by the opsonins. The blood to furnish the leucocytes and that to furnish the serum should be taken from a single puncture and at the same time.

To secure the blood it is best to encircle the thumb with a soft-rubber tube or with a bandage until marked cyanosis results, then make a puncture near the matrix of the nail, as shown in Fig. 70.

The blood that is to furnish the leucocytes is permitted to flow into a small test-tube ($2\frac{1}{2} \times \frac{3}{8}$ " in size) that has been about half filled with a 1.5 to 2 per cent. aqueous solution of sodium citrate. After the tube has been nearly filled, the blood and citrate are well mixed to prevent coagulation.



FIG. 71.—SPECIAL BLOOD PIPETTE FOR COLLECTING BLOOD FOR SECURING THE SERUM. (Miller.)



FIG. 72.—TUBE OF BLOOD AND CITRATE SOLUTION BEFORE AND AFTER CENTRIFUGALIZING. (Miller.)

The blood that is to furnish the serum is caught in a special pipette devised by Wright for the purpose, the shorter end of the tube being applied to the drop of flowing blood, which is at once taken up by a combination of capillary attraction and gravity. The blood in this tube is permitted to coagulate, which it does in a few minutes.

The tube containing the citrated blood is next placed in a centrifuge. To do this the blood need not be poured into a regular centrifuge tube, but the tube in which it is already contained can be placed in the metal centrifuge holder and packed around with cotton, the apparatus balanced with a similar tube, equally filled with water in the opposite arm, and then whirled until the corpuscles are completely sedimented, as shown in Fig. 72.

The citrated plasma is now carefully withdrawn with a pipette, *great care being taken that the corpuscles are not disturbed*, an equal volume of physiologic salt solution is added, and the tube shaken so that the corpuscles are

again distributed. After this the tube is again placed in the centrifuge and again whirled until the corpuscles are again sedimented, when the salt solution is removed with a pipette, the last drops being cautiously taken from the back of the meniscus, as shown in the illustration—



FIG. 73.—REMOVING LAST DROPS OF SALINE SOLUTION. (Miller.)

so that the corpuscles are not disturbed. The leucocytes are most numerous at the extreme upper layer of the corpuscular mass, where they appear as a very thin, superficial, pale, “creamy” layer.

After the blood in the serum tube has coagulated, the shorter curved arm is sealed in a pilot flame so as to leave a hook at that end, and the long, straight arm sealed off short. The tube is then suspended in the centrifuge tube, the hook caught over the edge of the tube, and a cotton packing placed around it to support it. The apparatus is then balanced and whirled for a few moments until the clot is thrown to one end and clear serum collected at the other. The tube is then scratched with a file or diamond just above the level of the serum, and broken so as to make it easy to collect the serum with a pipette.

The normal serum to be employed for controlling the test and calculating the opsonic index is secured from a normal individual—usually the operator himself—in precisely the same manner.

FIG. 74.—OPSONIZING PIPETTE CONTAINING BLOOD CORPUSCLES, BACTERIAL EMULSION, AND BLOOD SERUM. (Miller.)

Mixing the Factors and Making the Test.—It is always necessary to make two tests; one consists of a mixture of equal parts of the bacterial suspension, the washed corpuscles, and the *patient's* serum, the other of the bacterial sus-

pension, the washed corpuscles, and the *normal* serum. The method employed by Wright for this purpose is very ingenious and also quite simple. For the purpose a tube is prepared like that shown in Fig. 74.

A mark is made with a wax pencil about 1 cm. from the capillary end of this tube, to act as a guide in measuring the ingredient. Wright first draws in the "cream" from the blood corpuscle preparation, permitting it to rise to the mark, then draws in a minute bubble of air; then draws in the bacterial suspension to the mark, and admits another bubble of air; and finally draws up the serum to the mark. Thus the capillary tube contains, as shown in the illustration, three different ingredients in equal volume.

These are next mixed by cautiously blowing them in and out of the tube several times upon a glass slide, as shown in Fig. 75. They are finally drawn into the capillary tube so as to come to rest about a centimeter from its end, which is sealed in a flame.

Two such mixtures are prepared, one with normal serum, one with the patient's serum, and then both tubes, having been sealed, are placed in a thermostat at 37.5°C . for fifteen minutes in order that phagocytosis may occur. The exact length of the incubation makes little difference, provided that it be the same in all cases, so that uniformity of results be secured. Those engaged in elaborate investigations of this kind find it convenient to employ a special kind of thermostat shown in Fig. 76.

This has the advantage of not having the temperature changed by frequently open-

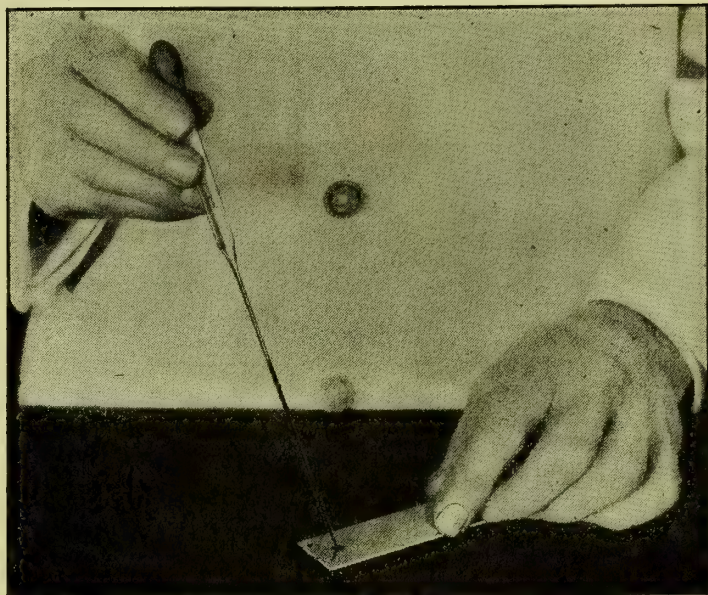


FIG. 75.—MIXING LIQUIDS BY REPEATEDLY EXPELLING ONTO SLIDE AND REDRAWING INTO PIPETTE. (Miller.)

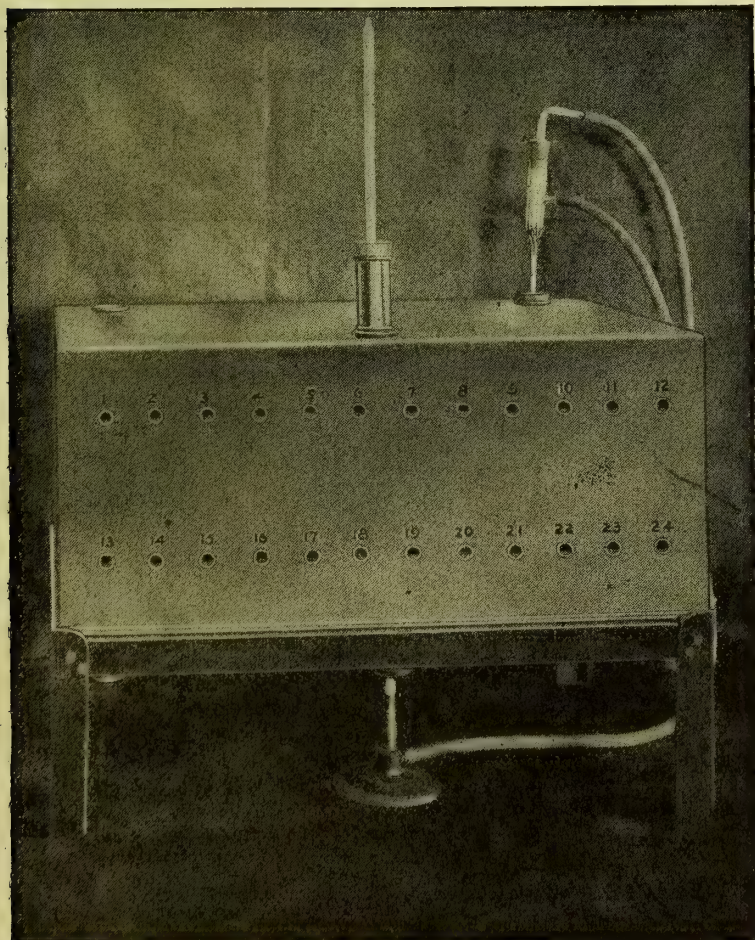


FIG. 76.—A SMALL INCUBATOR OF SPECIAL DESIGN FOR OPSONIC WORK. (Miller.)

ing and closing the doors, the tubes fitting into small tubular spaces, surrounded on all sides by the warm water of the bath.

When the period of incubation has ended, the tubes are withdrawn. Examination shows that the corpuscles have sedimented. They are then twirled between the fingers and thumbs for a few moments, so that the contents may

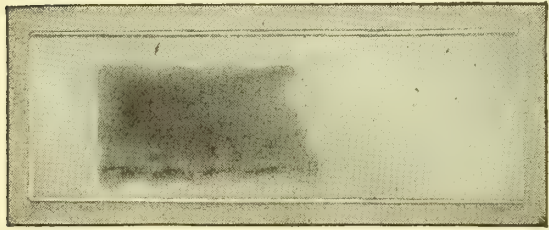


FIG. 77.—THE SMEAR. (Miller.)

be well mixed, the sealed end is broken off, and the contents expelled upon a slide and spread as an ordinary blood "smear." To be examined to best advantage this should be made by *pushing* the drop along the slide with the edge of another slide or a cover-glass. It is better when thick at one end and thin at the other, as shown in Fig. 77.

This film is next fixed and stained by any of the methods used for blood examination—Leishman's stain, Wright's stain, Jenner's stain, or Marino's stain. If tubercle bacilli are to be enumerated, carbol-fuchsin and acid solutions must be employed and followed by methylene-blue.

Enumerating the Bacteria and Calculating the Index.—This is a somewhat tedious matter, and is a crux of the method. The oil-immersion lens is used; the smear is given a hasty examination to determine in what part the leucocytes are most numerous, most perfect, and the bacteria in a condition to be enumerated with accuracy. Having found this, future attention is devoted to it alone and the counting begun. In estimating the pyogenic bacteria the polymorphonuclear cells alone are considered; in estimating phagocytized tubercle bacilli, attention must be paid to the lymphocytes.

The number of bacteria in twenty cells is counted and averaged. Some prefer to count the number in fifty leucocytes and average them, no doubt coming to more accurate results, but entailing an increased amount of labor. Only the perfect cells are counted, broken or otherwise imperfect cells being thrown out. A mechanical stage is an advantage, but is not indispensable. The cells are counted one after the other without regard to the many or few bacteria they contain, as the purpose is to determine the average number of bacteria per cell in the totality of the leucocytes.

This is done with both specimens—i. e., that made with the patient's serum and that with the normal serum—and in nearly all cases the two will not conform.

The "opsonic index" is calculated by dividing the average number in specimens prepared with the patient's serum by the average number in the preparation made with the normal serum.

If they should conform, the result will be 1, which is the normal index. If the patient's serum contain more than the normal quantity of opsonin, it will be $1 +$; if less than the normal quantity, it will be less than $1 - 0.8$ or 0.6 , for example.

An enormous amount of investigation has shown that in all cases in which active immunity has been conferred upon animals through experimental bacterination, phagocytosis is increased and the opsonic index increased, and the application of the method to human therapeutics shows that it is possible by

the same method of bacterination to raise the opsonic index, thus to accelerate and intensify phagocytosis and correspondingly benefit the patient.

One of the most important features of the thoroughness of Wright's work lies in his discovery that the bacterination of the patient is followed by a period during which the opsonic index is diminished. This constitutes the "*negative phase*," which soon gives place to a "*positive phase*" during which the index rises. The success of the bacterio-vaccination of any disease depends upon so conducting the treatment as to avoid negative phases and maintain a heightened opsonic index. It is for the determination of the condition of the patient with reference to these phases that the study of the opsonic index is advised, for it can be readily understood that if the bacterio-vaccine is administered in such large doses as to prolong or maintain the negative phase, in which phagocytosis is diminished, the patient is harmed instead of benefited by the treatment.

Inability to perform the opsonic test should not, however, militate against the employment of bacterio-vaccination, for enough work has been done to show about where the danger-point lies, and commercial houses now prepare and sell bacterio-vaccines of which a given volume contains a counted number of bacteria. They also furnish directions of a reliable nature, in which the calculated beginning and subsequent doses are given, so that the treatment may be conducted with good hope of success by those devoid of laboratory facilities.

There are, however, certain elements of success insisted upon by Wright. How valid they are will be shown by further experience. Thus, he insists that the vaccine be prepared from cultures obtained from the case to be treated, and also insists that the opsonic index be calculated after each administration of the remedy. This naturally makes it impossible for the average practitioner to conduct the treatment. Experience is showing by an abundance of evidence that it is possible to break away from these rules. It must not be forgotten, however, that the success of the method depends upon the immunization of the patient against the particular microörganism to be destroyed by the phagocytes, so that in beginning the treatment it is imperative to know with what microörganisms one has to deal. This is best achieved by a bacteriologic examination of matter taken from the lesion, yet in many cases experience has shown what bacteria are to be expected. Thus in acne and furuncle it is the staphylococcus in nearly all cases; in gleet it is the gonococcus; in post-typhoid abscess, the typhoid bacillus; in tuberculosis of the bones and joints, the tubercle bacillus, and so on.

It is, however, only fair to the originator of the method not to condemn it where its application has been made without attention to the requirements upon which he insists, and when this is done, and failure results, it is one's own application of it, and not the method in general that should be disapproved.

In reference to the dosage, it is advantageous to have some idea of the number of dead bacteria one may administer without inducing so marked a negative phase as to do harm. For this purpose Wright¹ tentatively suggests:

¹ Jour. Amer. Med. Assn., August 10, 1907.

Bacillus coli	5-50	millions.
Gonococci	5-50	"
Micrococcus neoformans	50-100	"
Pneumococci	10-50	"
Staphylococci	50-1,000	"
Streptococci	10-25	"
Typhoid bacilli	5-50	"
Bacillus pyocyaneus	5-50	"

G. M. Ross ¹ endeavors to systematize the affections remediable by means of bacterination or bacterio-vaccination thus:

A. Due to *Staphylococcus pyogenes*:

1. Furunculosis.
2. Pustular acne.
3. Sycosis.

B. Due to *Pneumococcus* of Fränkel:

1. Empyema.
2. Cystitis.
3. Suppuration of the antrum.

C. Due to *Bacillus coli communis*:

1. Cystitis.
2. Various local affections.

D. Due to the gonococcus:

1. Gleet.
2. Gonorrheal rheumatism.
3. Acute gonorrhea.

E. Due to the *Bacillus tuberculosis*:

I. Strictly Localized Tuberculosis.

1. Lupus and tuberculous ulceration of the skin and subcutaneous tissues.
2. Tuberculous diseases of the bones and joints.
3. Tuberculous cystitis.
4. Tuberculous nephritis.
5. Tuberculous epididymitis.
6. Tuberculous peritonitis.
7. Tuberculous adenitis.
8. Tuberculous laryngitis.
9. Tuberculous iritis.

II. Not Strictly Localized Tuberculosis.

1. Pulmonary tuberculosis.

To these may now be added:

F. Due to *Bacillus pyocyaneus*:

1. Localized infections.
2. General infection.

¹ Brit. Med. Jour., July 7, 1906, p. 16, ii.

G. Due to *Streptococcus pyogenes*:

1. Localized infections—appendicitis.
erysipelas.
2. Generalized infections—puerperal fever.

H. Due to *Bacillus typhosus*:

1. Typhoid fever.
2. Post-typhoid bacillary suppurations.

I. Due to *Micrococcus melitensis*:

1. Malta fever.

It would seem to be a useless tax upon the patience of the reader to enter upon a particular discussion of each of these groups. For all of those mentioned there is now considerable literature, a review of which would sometimes—as in the tuberculous cases—extend over several pages.

Regardless of the particular infection to be treated, the principle is the same: The bacterial specific for the infection should, when practicable, be secured from the patient himself; when impracticable, from the regular laboratory stock. Increasing doses are to be administered at intervals of several days, and when practical the effects are to be controlled by the estimation of the opsonic index. This, when impossible, is dispensable, and the merits of the treatment to be judged by the condition of the patient.

The single exception to this plan of action is found in the case of tuberculosis, where some prefer to inject the bacillary emulsion or true vaccine, others to use the old tuberculin, still others to employ other products of the bacillus.

All of these preparations seem to lead under judicious application to an increase in the opsonic index of the patient, and are, therefore, supposed, according to Wright's idea, to be of benefit in the treatment.

B. BY AIDING THE TOXIN-ENDURING POWER

a. *By Stimulating Antibody Formation During the Course of a Prolonged Infection. By the Injection of Bacterio-proteins.*—BACTERIOPROTEINATION—*Tuberculin, Leprolin.*

Tuberculin.—In 1890–1 the medical world was aroused to the greatest enthusiasm in consequence of a publication by Robert Koch ¹ regarding a culture product of the tubercle bacillus, to which he gave the name *tuberculin*. During the two decades that have followed, the product has met with every possible experimental employment and therapeutic application, and has gradually been narrowed down to a usefulness restricted to purposes of diagnosis, or to the treatment of early and uncomplicated cases of tuberculosis.

Koch found that when guinea-pigs are infected with tubercle bacilli the original wound heals readily and all signs of local disturbance except enlargement of the regional lymphatic nodes soon disappear. After about two weeks, however, a slight induration appears at the seat of original inoculation,

¹ Deutsche med. Wochenschrift, 1891, No. 343.

develops into a firm nodule, ulcerates, and remains open until the animal dies of the tuberculous disease. If a second infection be performed, the course of events is changed. The primary wound and the tissue surrounding it becomes dark in color and obviously necrotic, and eventually sloughs away, leaving an ulcer which rapidly cicatrizes and permanently heals.

The same effect was observed to follow whether the second inoculation was made with living or dead bacilli, and later was observed to follow when a glycerine extract of the tubercle bacillus cultures (tuberculin) was employed.

This tuberculin, also known as the "*Old Tuberculin*," is in nature an albuminous derivative, or bacterio-protein, extracted from the tubercle bacillus or from the media in which it has grown. It is not a toxin or a toxalbumin, as it is thermostabile and not destroyed by heating to 120° C., and is not poisonous to normal animals. It is, however, extremely destructive to tuberculous animals, causing a marked hyperemia about the tuberculous lesions, a pronounced rise of temperature, and in small animals with extensive lesions causing death if the dose administered be large.

The preparation of the old tuberculin, as conducted at the present time, differs from the original method of Koch, whose mode of extraction was to place great masses of bacteria from glycerine bouillon cultures upon a fine wire netting and pour diluted glycerine upon them again and again for the purpose of extracting the tuberculin.

At present flasks containing glycerine bouillon are inoculated with cultures and allowed to grow until the surface is covered with a bacillary pellicle. The flask is then gently shaken to permit the pellicle to sink, then again stood away in the thermostat to grow a new pellicle. This is repeated until no more surface growth can be secured, when the culture is declared to be "ripe." Many such flasks are then placed in a steam sterilizer and heated until the bacilli are all killed, after which the total contents—fluid and bacterial masses—are placed in a large evaporating dish over a water bath and evaporated, at a temperature as high as the boiling water will provide, to one tenth of the original volume. The thick, dark fluid thus secured is filtered through paper and then through a Berkefeld filter. This preparation of the old tuberculin is sometimes known as "*crude tuberculin*," to distinguish it from the next preparation made by Koch, which he called "*refined tuberculin*." This was made by adding to the crude product a volume and a half of absolute alcohol, stirring thoroughly, and standing aside for twenty-four hours. The flocculent precipitate was then secured by decanting the supernatant fluid and adding an equal volume of 60 per cent. alcohol. A second sedimentation is then permitted to take place, the fluid again decanted, and fresh 60 per cent. alcohol added, and so on several times, after which the precipitate receives one washing with absolute alcohol, and after a final sedimentation and decantation, is dried in an exsiccator. A whitish powder is thus secured which contains the active properties of the crude product in a much concentrated form.

The "crude tuberculin" prepared as above is also sometimes called the "concentrated tuberculin" in contradistinction to the "diluted tuberculin" commercially put out in a dilution of a 1 per cent. aqueous solution of carbolic acid, of which 1 c.c. equals doses containing stated measured quantities of the original product.

This "old tuberculin" should always be understood when the word tuberculin is used without any qualification.

It is unfortunate that the term "tuberculin" is at present carelessly employed to signify any culture product of the tubercle bacillus. The resulting confusion has theoretical importance as well as practical significance—for example, when the suspension of tubercle bacilli, to which Koch gave the name "*Bazillinemulsion*," which is a bacterio-vaccine, is thus confused with chemical products of the culture.

Other products of the tubercle bacillus that are closely related to tuberculin, if not identical with it, are the *Tuberculocidin* of Klebs (*Die Behandlung der Tuberkulose mit Tuberculocidin*, 1892), and its close relative, *Antiphtthisin* of Klebs, though these contain, in addition, comminuted bacillary fragments. Also there seems to be no essential difference between the culture furnishing the tuberculin and the "Bouillon filtré" of Denys,¹ except that no heat is used in the preparation of the latter—a matter upon which its originator lays great stress.

Koch continued his work upon the tubercle bacillus and its products after an interim, and in 1897 (*Deutsche med. Wochenschrift*, 1897, No. 14) published an account of a new substance, to which the name "*Tuberculin R*" has been applied. It is essentially dissimilar from the old tuberculin in that it is not a culture product, but a bacillary product. That is to say, the original or old tuberculin consisted of such substances as were spontaneously eliminated from the bacilli or were extracted from them by the aid of heat and glycerine; the new product, "Tuberculin R," embraces only the endotoxins of the bacilli, and contains none of the soluble products. It is, therefore, more nearly related to the bacterio-vaccines, and comes nearly in the group to which the term "free receptus" has been applied.

The nature of the preparation is made clear by an examination of the method by which it is made. Koch worked with the living, virulent tubercle bacilli, which he first dried thoroughly and then carefully crushed in an agate mortar. Very small masses of the dry bacilli were treated at a time, and the process of comminution was made as complete as possible. Having reduced all of the bacilli to fragments, he placed them in distilled water, thoroughly washed them, and recollected them by centrifugation, as a muddy sediment at the bottom of the tube elsewhere filled with a clear opalescent fluid. For convenience he called the fluid TO, the sediment TR. The TO was found to contain tuberculin. The fragments were next removed, thoroughly dried, and again triturated in the agate mortar, redistributed throughout distilled water, and again collected by centrifugation. After the second centrifugation microscopic examination showed that the bacillary fragments had not yet been resolved into a uniform mass, for when the TO was subjected to staining with carbol-fuchsin and methylene-blue, it was found to exhibit a blue reaction, while in TR a cloudy violet reaction was obtained.

The addition of 50 per cent. of glycerine had no effect upon TO, but caused a cloudy white deposit to be thrown down from TR. This last reaction

¹ Acad. royale de méd. de Belgique, February 22, 1902; *Centralbl. f. Bakt. u. Parasit. Ref.* 7, 1902, xxxi, p. 563.

showed that TR contained fragments of the bacilli insoluble in glycerine. In making TR, Koch advises the use of a fresh, highly virulent culture not too old. It must be perfectly dried in a vacuum exsiccator, and the titration, in order to be thorough, should not be done upon more than 100 mg. of the bacilli at a time. A satisfactory separation of TR from TO is said only to occur when TO takes up at least 50 per cent. of solid substance, as otherwise the quantity of TO in the final preparation is so great as to produce undesirable reactions.

Such is the method, now greatly modified by commercial enterprise, by which Koch endeavored to separate the irritating and offensive tuberculin-containing factors TO from the immunizing and inoffensive factors TR.

Experiments upon guinea-pigs showed that TR had decided immunizing properties independent of any febrile reactions such as were shown by the old tuberculin and its derivatives.

The reader will perceive that in discussing tuberculin and its related preparations a change of base is inevitable. We begin with tuberculin, an extractive and bacterio-protein, and end with a bacterio-vaccine.

In 1901 Koch¹ published a report upon certain experiments directed toward the diagnosis of tuberculosis by making use of the phenomena of agglutination (modified Widal reaction), in the course of which he found that the bacillary suspension employed, when injected into experiment animals, not only produced a marked increase in the agglutinative property of the blood serum, but also seemed to possess distinct immunizing and some curative powers. These observations led to a considerable investigation of the new product (really a bacterio-vaccine) under the name "*Bazillenemulsion*."

In 1904-5 Spengler² called attention to the dissimilarity of human and bovine bacilli, and to the fact that their products might not be interactive. He therefore proceeded to prepare a "Perlsucht" bacillus tuberculin—i. e., a tuberculin comparable to Koch's old tuberculin, using the "Perlsucht" or bovine bacillus instead of the human bacillus almost universally employed for the other because of its greater facility of growth.

With these numerous and dissimilar products to consider, it were indeed a difficult task, in the scope of a paper of the length to which this must be restricted, to enter upon an adequate discussion of their respective therapeutic merits, especially as there is no single one upon which there is anything like a uniformity of opinion.

Leprolin.—Rost³ thought that he had succeeded in cultivating *Bacillus lepræ* upon a medium prepared by distillation to free it from sodium chloride. Whether the bacillus cultivated be the lepra bacillus or not is somewhat doubtful. Whatever it was, Rost cultivated it, and from the cultures prepared a substance much according to the general plan upon which old tuberculin is prepared, and called it *Leprolin*. With this he treated a number of lepers at the Leper Hospital at Rangoon, Burmah, many of whom are said to have been greatly benefited, and some cured.

No confirmation of Rost's work has yet appeared.

¹ Deutsche med. Wochenschrift, 1901, No. 48, p. 829.

² Ibid., 1904, No. 31; 1905, Nos. 31 and 34.

³ Brit. Med. Jour., February 22, 1905; Indian Med. Gazette, 1905.

2. BY INDUCING PASSIVE IMMUNITY

A. BY NEUTRALIZING TOXINS PRODUCED IN THE BODY

By the Injection of Antitoxic Serums.—ANTITOXINATION—*Diphtheria, Tetanus, Snake Bite, Hay Fever, Plague, Tuberculosis, Typhoid Fever.*

Antitoxic Serums.—The antitoxic quality of the blood serum of immunized animals makes its appearance in those cases in which a toxic antigen (toxin) has been administered in increasing doses in such manner as to effect successive and increasing reactions, resulting in the elimination of free receptors from the cells and their appearance in the body fluids, notably the blood.

There can be no doubt about the chemical nature of the toxin-antitoxin reaction, though the visualization given in Ehrlich's diagrams and his use of the terms receptor and haptophore were intended to assist in appreciation of the process when its nature was regarded as unique. Receptors and haptophores must now be thought of as molecular combinations not differing essentially from other chemical combinations.

As has been shown in the introductory summary of the phenomena of immunity, the antitoxic serums differ from a large number of antiserums only in their toxin neutralizing power. They are, however, *combining serums*, whose peculiarity is combination with and consequent inhibition of the physiological action of the particular active substance—antigen—through whose stimulation they were formed.

These serums being essentially the same in function, whether antitoxic, antienzymic, anticoagulant, antiagglutinative, or antimicrobial, are all formed through the discharge of the excessive receptors into the blood. It matters not how their subsequent function is performed, whether by direct and immediate combination, as is conceived to be the case with the antitoxins, or by indirect or intermediate reactions such as are conceived to be the case with the antimicrobial serums, the mode of preparation is the same; all depend upon the presence of free receptors; the only difference is in the nature and function of the antigen.

It is further to be remembered that the receptors regenerate, become excessive and detract from the cell (Weigert's addition to Ehrlich's theory) because of the adaptation and affinity of the haptophores for the receptors. The toxophores have nothing to do with it, and highly active combining serums, such as antitoxins, may be formed where the toxophores are inactive or have been destroyed. They may also be found in animals immune against the toxophores. Thus Metchnikoff has found that the alligator is insusceptible to the action of certain toxins, yet upon repeated injection of those toxins forms good antitoxins.

In many cases, however, the only method of knowing how much haptophorous substance is present in a culture is by estimating the toxophorous molecules. This applies to both diphtheria and tetanus toxins.

Preparation of the Antitoxic Serums.—This is a very simple matter and needs no lengthy description. In the case of the antidiphtheritic and antitetanic serums the ground has been so well covered experimentally that the

path to success can be traveled with certainty. Certain elements contributing to success must, however, be considered. Thus, it is first necessary to secure an appropriate antigen. In ordinary experiments, where principles are to be established or new facts discovered, this is less necessary than in commerce; where a known fact is to be applied to the best possible economic advantage and in competition with others, this becomes a matter of importance, so that much attention has been paid to it. The toxin used for the immunization of the animals that are to furnish the serum must be as rich as possible in haptophorous units. For this purpose it is customary to select one that shows itself rich in toxophorous units. Experience with many cultures has shown that they differ decidedly and that some yield more useful antigens than others, though the difference is not fully understood.

The culture of the diphtheria bacillus, shown by experience to be appropriate, is grown in bouillon of an appropriate reaction, and devoid of sugars, until the highest degree of toxicity is secured—usually about six to eight days. The bacilli are then killed by the addition of an antiseptic, and the culture filtered through a Berkefeld filter to remove the dead organisms. This constitutes the toxic bouillon, or “toxin.”

It is important to choose an appropriate animal to furnish the serum, for it should be obtainable in sufficient quantities to make the production practicable on a large scale. After experiments upon many animals the horse was finally selected. Its advantages are that it does not suffer from diseases communicable to man, that its serum is usually inoffensive to the human organism, that the serum obtained from the blood is clear and limpid, and that large quantities are easily obtainable.

The horses selected for immunization are healthy animals of good size. They are examined with great care to determine their freedom from infectious and constitutional diseases.

The immunization treatment is carried on by slightly different methods by various workers in various places, and has been subjected to slight modifications from time to time. Whatever the method, the principle is the same, and as the reactions effected are of a physiologico-chemical nature they cannot be greatly modified. The method, when reduced to its most simple form, consists in the administration of a succession of subcutaneous injections of the toxin, beginning with a very small dose and increasing as rapidly as is consistent with the maintenance of perfect health in the experiment animal. Following each injection there is a reaction—i. e., a physiological reaction—which results in the addition of antitoxin in the blood. These increases usually bear a fair mathematical relation to the quantity of the toxin injected. Excessive reactions with adverse symptoms, such as much fever, etc., are to be avoided, though local reactions with great swelling of the tissues seems to be inevitable.

The period of treatment varies with the exact method, but always requires a number of weeks.

When the blood, which is subjected to frequent tests, is shown to have acquired a sufficient degree of antitoxicity, the horse is bled by introducing a cannula into the jugular vein and conducting the blood through a sterile tube into appropriate sterile receptacles.

The subsequent methods vary. If the serum is to be employed in its original form, the blood is permitted to coagulate, then stood away until the clot retracts and the clear serum can be pipetted off into sterile receptacles. It then receives an addition of some antiseptic, carbolic acid or trikresol being generally employed, the purpose being to prevent subsequent contamination; is filtered through a Berkefeld filter to remove the unsightly precipitate thrown down by the antiseptic, and having had its activity accurately calculated, is bottled for use.

In case the serum is not desired, but the "proteid precipitate" to be prepared, the blood is collected in vessels containing some sodium-citrate solution, by which its coagulation is prevented. The citrated plasma having been secured, it is then treated by a method suggested by Gibson.¹ The diluted citrated plasma is first treated with an equal volume of a saturated aqueous solution of sodium sulphate, and the globulins, with which the antitoxic principle is thrown down, collected upon a filter paper. The precipitate is next extracted with a saturated solution of sodium chloride and the soluble antitoxic proteins reprecipitated from the saturated sodium-chloride solution with acetic acid. This precipitate is caught upon paper filters, partly dried by being pressed with other filter papers, and then dialyzed in running water. This yields a product which, when dried *in vacuo*, is soluble in physiological salt solution, and is supposed to be free from any offensive substances that might have been present in the original serum.

The estimation of the antitoxic value is a matter of some complexity, and is of purely technical interest. All laboratories now make their estimations according to the method devised by Ehrlich, his standard having been adopted by the Hygienic Laboratory of the United States Public Health and Marine Hospital Service, by which the work done in all laboratories in this country is now controlled, so that perfect uniformity as well as reliability of the products prevails. There need no longer be any apprehension regarding the quality of the products commercially marketed in the United States, or any misgiving that the statements on the labels are not correct. (Bulletin No. 21, U. S. Public Health and Marine Hospital Service, Washington, D. C., 1905.)

The serum is quite stable, losing only 50 per cent. of its strength after being bottled for two years. There is distinct advantage in not using serums that are too fresh, as the patients are less apt to be troubled with the by-effects of the serum itself.

Having thus covered the ground from the theoretical point of view, in a manner applicable to any serum falling within this group, only brief mention need be made of the particular serums belonging to the group.

Antidiphtheritic Serum.—This was first made and utilized for the practical treatment of diphtheria in human beings by Behring.² It immediately attracted attention throughout the medical world, and has given rise to an enormous literature, to review which would be useless. It has had a wide-

¹ Jour. Biol. Chemistry, i., p. 161; iii, p. 253.

² Deutsche med. Wochenschrift, 1890, Nos. 49-50; Zeitschrift für Hygiene, etc., 1892, xii, p. 1; Die Blutserumtherapie, Berlin, 1902.

spread application, has stood the test of twenty years of painstaking investigation, and has established itself as the only treatment of diphtheria upon which any reliance can be placed. The question of its value is no longer discussed: it is proven. The only contributions of recent date have to do with improvement in its preparation and in the method of administration.

The serum acts by virtue of its toxin-neutralizing power, not by any known stimulation of the bacteria-destroying mechanism. It confers only a passive immunity that persists so long as the antitoxin escapes elimination, which appears to be a matter of a few weeks. The toxin being neutralized, no further local destruction of tissue can be effected in the throat, the bacilli there present no longer prepare a poison by which the central nervous system is depressed, and the patient's other defensive mechanisms attack the microorganisms successfully, so that rapid recovery is usually effected.

The remedy is always administered by subcutaneous injection, though in severe cases intravenous administration is to be preferred as resulting in more prompt action. It is useful both for prophylaxis and for treatment. For prophylaxis 500 to 1,000 units should be administered; for treatment not less than 1,000 units should be given even to a small child. The exigencies of the case must determine the size of the dose. The chief mistake is to err on the side of stinginess. In bad cases, and especially in late cases, 4,000 to 5,000 units should be prescribed at a dose, and the dose given into a vein. Frequent large doses have not infrequently saved life when every aspect of the case seemed hopeless.

Statistics from all parts of the world agree in showing that the mortality from diphtheria in the preantitoxic period was more than 30 per cent.; in the postantitoxic period, less than 10 per cent.

An occasional fatality after the employment of the antidiphtheritic serum for prophylaxis seems to be inevitable, or of difficult prevention. The patients, being in apparently perfect health and receiving injections for the purpose of preventing diphtheria when exposure to infection has occurred, sometimes are taken within a few minutes with peculiar symptoms—irregularity of cardiac action, sense of suffocation, swelling and itching of the face, cyanosis, intense prostration, and die in a few minutes. Very few such fatalities have been reported, but they are of great interest and have been made the subject of much thought and experimental research.

The accidents seem to fall into a group of phenomena first pointed out by von Pirquet and Schick,¹ and called by them the "Serum disease." This peculiar affection consists of urticarial eruption, erythema, pain in the bones and joints, fever, swelling of the lymph nodes, edema, and albuminuria. The symptoms usually appear after an incubation period of eight to thirteen days, but may come on immediately after the injection of the serum. Death appears imminent, and may occur in very rare instances.

In 1905 Rosenau and Anderson² studied it with great energy and fertility

¹ Die Serumkrankheit, Leipsic and Vienna, 1905.

² Jour. Med. Research, 1906, xv, p. 207; Bull. Nos. 29 and 36 of the Hygienic Laboratory of the U. S. Public Health and Marine Hospital Service, 1906 and 1907; Jour. Med. Research, xvi, No. 3, p. 381; Jour. Infectious Diseases, iv, No. 1, p. 1, 1907, and iv, p. 552, 1907.

of thought from the experimental point of view. It was also made the subject of careful study by Gay,¹ Gay and Southard,² and others.

The phenomena are described as "hypersensitivity," and are specifically described as *Anaphylaxis*. The researches of Rosenau and Anderson show that they are in no sense peculiar to the action of the antidiphtheritic serum, but pertain to normal horse serum, indeed, to any serum, or, in fact, to any heterologous proteid with which any animal is injected according to a given experimental plan. Thus, if a guinea-pig be given an experimental injection of say $\frac{1}{250}$ c.c., or less, of horse serum, no visible change is provoked, but the effect of the injection is a profound physiologico-chemical disturbance that is not completed for about twelve days. This disturbance characterizes the sensitization and makes the animal peculiarly subject to disturbance if at any subsequent period of its life it should again receive horse serum. Thus if, after this primary sensitization is effected, the guinea-pig be given a dose of $\frac{1}{10}$ c.c. of the same serum, it almost immediately becomes profoundly distressed, extremely uneasy, pants for breath, violently scratches its face and head, soon falls to the ground, gasps for breath, and may die within an hour. When the body of such an animal is examined, it is found that widely distributed minute hemorrhages pervade the tissues, that the mucous membrane of the stomach is ulcerated, and that the nervous system is much injured.

The guinea-pig is particularly susceptible to the anaphylactic reactions, as is well exemplified by tuberculin. It is well known that although normal guinea-pigs are not injured by tuberculin, those with well-marked tuberculous lesions are quickly killed—a reaction of anaphylaxis.

In the absence of other explanations of the serum disease it seems best to regard them as falling within this group of physiological disturbances, particularly as it is the usual experience to find the symptoms in those treated with serum during second attacks of diphtheria, or those in whom injections of the serum follow one another at long intervals.

To connect the cases of sudden death with prophylactic injections is more difficult, since no primary sensitization can be accounted for, yet their symptomatology is such as to have little doubt of their being obscure anaphylactic reactions.

Antitetanic Serum.—This was first prepared and used by Behring and Kitasato.³ It conforms, in general, both in method of preparation and in mode of action to the antidiphtheritic serum, though certain divergences must be mentioned. In the first place it exemplifies the fact that when the antigen is composite in composition, the antibody will be similarly composite. Thus it is known that the tetanus toxin (toxic bouillon) contains at least two principles, known respectively as tetano-spasmin and tetano-lysin. The antiserum contains principles that antagonize both of these. The former, the antitoxin discovered by Behring and Kitasato, the latter an antilysin discovered by Madsen.⁴ It is naturally advantageous for the therapeutic serum to contain principles that antagonize all of the activities of the metabolic products of

¹ Jour. Med. Research, xvi, No. 2, p. 143, 1907.

² Ibid., xviii, No. 3, p. 385, 1908.

³ Deutsche med. Wochenschrift, 1890, No. 49.

⁴ Zeitschrift für Hygiene, etc., 1899, xxxiii, p. 239.

the specific organism. Indeed the antidiphtheritic serum is probably a composite of various antibodies opposed to various ingredients of the toxin that have not yet been separated, and Martin has been inclined to assign much of the virtue to effects other than those purely antitoxic. The opinion has not been substantiated.

The serum is prepared along lines that exactly parallel those of the antidiphtheritic serum. The bacillus of tetanus being anærobic, must, of course, be grown under appropriate conditions of anærobiosis, reaction, and temperature until its greatest activity is attained. The culture after being filtered and otherwise treated is injected into horses in precisely the same manner as for the preparation of the other serum, and when the tests of the blood show sufficient potency, the horse is bled and the serum prepared in exactly the same manner. The tests for determining the potency are also conducted according to standard methods devised and controlled by the Hygienic Laboratory of the U. S. Public Health and Marine Hospital Service, and to-day there is uniformity in the terms given all of the commercial serums.

The antitetanic serum fulfils two requirements: first, prophylaxis, for which it appears to be perfectly satisfactory; second, treatment, for which it is not infrequently inefficient.

It may be safely conjectured that if the serum could be applied in all wounds infected with the tetanus bacillus scarcely any deaths from tetanus would occur, but in the generality of wounds the physician or surgeon is culpable because of a false economy that makes him hesitate to "waste" a little serum when it may not be needed. It is, of course, difficult to obtain comparative statistics upon human beings because prophylaxis is carried on in such a desultory fashion, but the experiences of those engaged in veterinary surgery are convincing, and should emphasize the importance of prophylaxis in human medicine.

In a large institution with which the writer of this paper was connected, and in which more than eight hundred horses came under observation for a variety of operative manipulations, the death rate from tetanus at one time amounted to 10 per cent. After the prophylaxis with antitetanic serum was introduced as a routine precautionary measure it fell to less than 1 per cent.

In considering the utility of the antitetanic serum in therapeusis we are immediately confronted with the difficulty of obtaining accurate statistics, for cases of tetanus have not been systematically reported, deaths after antitetanic serum are sometimes published, sometimes not, and cases recovering after the employment of the serum are very commonly reported. A further and more serious source of embarrassment was the lack of uniformity in denominating the unit strength of the serums prior to the introduction of the standard unit by the Hygienic Laboratory of the U. S. Public Health and Marine Hospital Service in October, 1907.¹

The difficulty in effecting a cure in cases of tetanus depends upon the fact that the toxin possesses so marked an affinity for the motor cells of the nervous system that they are already profoundly impressed by the time the symptoms of the disease manifest themselves. This is well exemplified by the experiments

¹ Treasury Circular, No. 61, October 25, 1907.

of Nocard, who says: "Take three sheep with normal tails and insert under the skin at the end of each tail a splinter of wood covered with the dried spores of the tetanus bacillus; watch these animals carefully for the first symptoms of tetanus, then amputate the tails of two of them 20 cm. above the point of inoculation . . . the three animals succumb to the disease without showing any sensible difference."

This shows that by the time the earliest symptoms appear enough toxin is present in the blood to cause death. When the blood is withdrawn from an animal suffering from tetanus it is found to contain enough toxin to poison mice with the typical symptoms. In all cases of tetanus, then, we begin operations when the quantity of toxin in the blood may be fatal, and when it may already be firmly anchored to the ganglionic cells. That death must be inevitable in human beings because symptoms of the disease have appeared is untrue, for about 20 per cent. of cases of tetanus recover without specific treatment.

The fundamental principles upon which the administration of the antitetanic serum is conducted have to do, first, with the neutralization of the toxin in the patient's blood, and second the hope of detaching that anchored to the nervous system.

The utmost importance attaches to the immediate application of the serum. Dönitz¹ found that if a mixture of toxin and antitoxin were made before injection into an animal, twelve minimal fatal doses could be neutralized by 1 c.c. of a 1 to 2,000 dilution of an antitetanic serum with which he was experimenting. If the antitoxic serum was administered four minutes after the toxin the strength of the dilution had to be increased to 1 c.c. of a 1 to 600 dilution; if eight minutes after the toxin, to 1 c.c. of a 1 to 200 dilution, and if fifteen minutes after, to 1 c.c. of a 1 to 100 dilution. These experiments show how quickly the toxin fixes itself to the cells.

The administration should consist of a large dose, given into a vein, and repeated frequently so long as the symptoms persist. The endeavor to accelerate the rapidity and effectiveness of the serum by injecting it into the subdural space and into the spinal canal has not been sufficiently successful to warrant so serious an operation as that of trephining. The blood carries the serum to the nervous tissues very quickly, and it is not certain that the effective reaction takes place elsewhere than in the blood. It is not known that the toxin-nerve-cell combination once effected can be dissolved, though it is theoretically possible; it is known that the toxicity of the poison in the blood can be neutralized and prevented from effecting further attachment to the nerve cells.

The first extensive analysis of cases of tetanus treated with the antitetanic serum was made by Moschcowitz,² who found that the use of the serum had to all appearance reduced the death rate from 80 to 40 per cent.

Lambert³ collected interesting statistics upon tetanus, showing a mortality variation in acute cases from 78 to 96 per cent., with an average of 88 per cent.

¹ *Deutsche med. Wochenschrift*, 1897, p. 430.

² *Annals of Surgery*, 1900, xxxii, No. 2, pp. 219, 416 and 567.

³ *Medical News*, 1900, July, p. 12.

In chronic cases the average mortality was found to be about 40 per cent. Of 1,226 cases occurring during the war and collected through the War Department the mortality was 88.6 per cent.; of 280 cases in time of peace, the mortality was 76 per cent. These general statistics serve to show the accuracy of Moschcowitz's collection, in which 80 per cent. figures as the death rate in cases not treated with the serum. Lambert continues with statistics upon the tetanus serum, showing that of 262 collected cases, 151 recovered, the mortality being 42.36 per cent., thus again confirming Moschcowitz's figures. Of Lambert's cases 124 were acute, of which 35 recovered, the mortality being 71.77 per cent.; 138 were chronic, 116 recovering and giving a mortality of 15.94 per cent. His final conclusions are highly favorable to the employment of the antitetanic serum which, he declares, has reduced the death rate in the totality of cases to about 24 per cent.

These exceedingly favorable results were obtained at a time when there was no uniformity in the potency of the serum, when there was no consensus of opinion as to the dosage, and much personal opinion upon the mode of administration. If under such adverse conditions such results were possible, far better results may be expected under the exact methods that obtain at the present time.

The serum is at present marketed in packages containing 1,500 units (government standard), which is to be regarded as a single standard dose. Less should never be given, and this standard dose should be repeated frequently as the progress of the case suggests.

The dry serum is also combined with antiseptic powders and used with some success for prophylaxis by dusting it freely upon the wound.

Antivenomous Serum or Antivenene.—This serum was the outcome of experiments made by Phisalix and Bertrand¹ with viper venom, and by Calmette.²

The former observers developed some interesting facts of technical interest; the latter by a different method endeavored to reach practical results. Calmette, however, came to the erroneous conclusion that the neurotoxic principle of all venoms was the same, and that an antivenomous serum prepared by immunizing animals against the venom of the cobra, in which the neurotoxin predominated over all other elements, would be beneficial in the treatment of the bites of all serpents. Many exceptions have been taken to Calmette's work, the most important contributions coming from Tidswell and from Lamb, who showed that Calmette's commercial serum was without effect in combating the venoms of the Australian snakes, *Holocephalus curtus*, or the Indian snakes, *Bungarus cæruleus* and *Echis carinata*. It is also useless to stay the intense locally destructive effects of the American "pit vipers," especially the rattlesnakes.

Thus the utility of Calmette's serum is restricted to the treatment of cobra bites, and in a few cases actual demonstrations of its efficacy in saving human life have been made. These, together with much interesting matter upon the

¹ Compt. rendu. de l'Acad. des Sciences, Paris, February 5, 1894, T. cxviii, p. 356 et seq.

² Compt. rendu. de la Soc. de Biol. de Paris, 1894, February 10.

subject, may be found in Calmette's book, *Venoms; Venomous Animals and Antivenomous-Serum-Therapeutics*.¹

The practical experiments mentioned, together with the experiments of Flexner and Noguchi,² Noguchi,³ Madsen and Noguchi,⁴ have shown that not only do the venoms of different serpents differ in the varying proportions of the *hemorrhagin* and *neurotoxin* they contain, but in differences in the active principles themselves, so that there is small hope of securing any serum efficacy in treating the bites of all venomous animals, as Calmette originally supposed.

Noguchi prepared anticrobalus, antimoccasin, and other antivenomous serums on an experimental scale, but not in strengths worthy of practical application or in quantities meriting commercial production. The results of Noguchi's experiments are to be found in his book just appearing among the publications of the Carnegie Institution.

The antivenomous serums, with the exception of Calmette's, which seems useful for the treatment of cobra bites, are therefore of scientific interest rather than of practical value, and are not made commercially.

The reasons are the small number of persons bitten, the isolation of the bitten patient, and the improbability that one could be provided with the appropriate serum at the moment of necessity.

Polantin, or Hay Fever Antitoxin.—This was an attempt on the part of Dunbar⁵ to make a practical application of facts gleaned by a prolonged and thorough study of hay fever. Dunbar investigated the relation of pollen to hay fever, and seems to have connected it quite convincingly with the pollen of rye and other grains in Europe, and the pollen of the golden-rod (*Solidago*) in America. Finding it possible to extract a toxin from rye pollen that immediately precipitated an attack of hay fever when applied to the conjunctiva of a susceptible individual, he used it for the immunization of animals. When the immunization reached a certain point the animals were bled, the serum separated, and from it a powder prepared and compressed into small tablets. When these were simultaneously applied to the conjunctiva with some of the active toxin, no reaction followed. When patients suffering from hay fever received the tablets or had instillations of solutions of the "polantin" made into the conjunctiva the symptoms sometimes became greatly ameliorated.

In practical application the remedy has proved disappointing because of the fact that the conjunctiva is being constantly irritated by fresh pollen and inflames so soon as the temporary effect of the polantin is gone, and perhaps because different individuals may be susceptible to different varieties of pollen not neutralized in their irritative properties by "polantin" made by Dunbar's method.

The "polantin" is a commercial preparation.

Antituberculin and Antitubercle Serums.—Many attempts have been made to render the principles of antitoxic therapy applicable to the treatment of tuberculosis, but without result. Of those falling in this group the *tuberculin*

¹ London, John Ball, Sons & Danielsson, Ltd., 1908.

³ Ibid., viii, p. 614, 1906.

² Jour. of Exp. Med., vi, p. 277, 1901-1905.

⁴ Ibid., ix, p. 18, 1907.

⁵ Zur Ursche und Spezifischen Heilung des Heufiebers, München und Berlin. R. Aldenbourg, 1903.

of Koch was supposed to be the essential toxic product (antigen) of the tubercle bacillus against which the immunization of the experiment animal must be effected in order that the antitoxin—i. e., *antituberculin*—might be secured. The first to investigate the subject appear to have been Tizzoni and Centanni,¹ who were followed by Bernheim,² Paquin,³ Viquerat,⁴ and McFarland.⁵ Each of these investigators thought he saw prolongation of life in guinea-pigs and improvement in patients treated with the serum, but the benefits conferred were not such as to warrant the continuance of the treatment, so that all have passed into oblivion, and probably with justice, since in all probability the antituberculin is formed through the stimulation of an antigen not concerned in the process by which tuberculosis is to be combated.

A departure took place at the hands of Fisch,⁶ who employed Tuberculin-R for the purpose of immunizing the experiment animal. This seems to be a proper antigen for stimulating the production of bacteriolytic amboceptors and should find its proper mention below.

A second departure took place at the hands of Marmorek, who came to the doubtless correct conclusion that tuberculin is not the substance produced in the body by the activity of the tubercle bacillus. He accordingly set about the preparation of the real toxin, and found that by cultivating an appropriate tubercle bacillus in a bouillon made of liver instead of muscle, and receiving an addition of leucocytic serum, it was possible to obtain a new toxic product. This was used for immunizing horses from which a new antitubercle serum—*Marmorek's serum*—was obtained. The inventor and many of his supporters claim most encouraging results from its employment, but the serum has not become popular. It is commercially manufactured in France.

Typhoid Antitoxin Serum.—Chantemesse⁷ prepared a toxin, supposed to be a specific product of the typhoid bacillus, by growing the organism in a medium consisting of macerated spleen to which defibrinated human blood was added. After the cultures had grown for five to six days they were filtered. Of the filtrate 1 c.c. was found to be fatal when introduced into the abdominal cavity of an 80-gram guinea-pig. This "toxin" formed the basis of the immunization experiments which were performed upon horses. The serum obtained from the horses was thought to exert a marked curative effect. In a later paper Chantemesse⁸ reports results following the use of the serum in 507 cases of typhoid fever with a mortality of 6 per cent. The death rate was not diminished sufficiently to convince many physicians of the efficacy of the treatment.

An antityphoid serum made by the use of an endotoxin, and called an antiendotoxic serum, was used in 9 cases with seeming benefit by Hewlett,⁹ in 26 cases by Goodall (same reference), who saw benefit in only 9 cases in

¹ Centralbl. f. Bakt., etc., xi, p. 82, 1892.

² Ibid., etc., xv, p. 654, 1894.

³ New York Medical Record, 1895.

⁴ Centralbl. f. Bakt., etc., xx, Nos. 18, 19, p. 674, November 5, 1896.

⁵ Jour. Amer. Med. Assn., August 21, 1897.

⁶ Ibid., October 30, 1897.

⁷ Verhandl. d. g. Internat. Kongress für Hyg. & Demog., 1898.

⁸ Presse méd., 1902, No. 103.

⁹ Royal Society of Medicine, May 25, 1909. See Brit. Med. Jour., June 5, 1909, p. 1358.

his series, and in 5 cases by Bruce, who thought that 2 had been benefited. The results do not seem worthy of further attention.

B. BY INCREASING THE BACTERIA-DISSOLVING POWER OF THE BLOOD BY INJECTING A SERUM RICH IN SPECIFIC BACTERIOLYTIC AMBOCEPTORS FOR THE RESPECTIVE MICROBES TO BE OVERCOME.

ANTIMICROBINATION—*Erysipelas, Scarlatina, Puerperal Fever, Sepsis, Plague, Pneumonia, Tuberculosis, Gonorrhæa, Dysentery, Typhoid Fever, Cerebro-spinal Fever.*

The Antimicrobial or Bacteriolytic Serums comprise a class of immune products whose activity is to be referred to the presence of bacteriolytic or other specific amboceptors by virtue of which the dissolution of the respective microbes is supposed to be facilitated.

The difference between these serums and the antitoxic serums lies in the different character of the antigen. In the antitoxic serums the antigen is the specific toxic product; in the antimicrobial serums it is the whole culture, containing all the products, endotoxic as well as exotoxic. Upon purely theoretical grounds this should afford an antibody whose function should be that of an amboceptor only. As a matter of fact, however, the products are complex, for in the total culture there must be a variety of antigens, such as true toxins, toxalbumins, enzymes, etc., each of which occasions the formation of its specific antibody. This complex nature of the resulting antibody formation and mixed character of the serum, which must contain antitoxins, specific amboceptors, antienzymes, etc., makes it a difficult matter to foretell exactly what the therapeutic action of any such serum shall be.

In considering the matter it may be well to begin upon the assumption that the virtue of the antimicrobial serum resides in its content of specific amboceptor units.

These are, of course, concerned only in bacteriolysis, and act through the indirect combination of complement and microorganism. This combination can be shown by experiment to be a definite quantitative reaction. The preponderance of complement over amboceptor is of no advantage because the complement cannot attack the microorganism in the absence of amboceptors; the preponderance of amboceptor is useless if no complement is available for effecting the antimicrobial action; the preponderance of the microbes over both complement and amboceptor continues the infectious process.

Upon purely theoretical grounds the conclusion would be justified that the introduction of immune serum containing specific amboceptor units could be of no benefit beyond the point of satisfying the combining affinities of the available complement, and there is experimental evidence to show that their introduction is not only of no benefit, but of distinct detriment when this point has been exceeded. Thus, Neisser and Wechsberg¹ have shown that an excess of amboceptors results in a peculiar deviation of the complement (Ablenkung)—the “Neisser-Wechsberg phenomenon.” This phenomenon is

¹ München. med. Wochenschrift, xlviii, No. 13, p. 697, 1901.

based upon experiments that show that great superfluity of amboceptors diminishes the bacteriolytic activity, and upon the assumption that the inhibition of bacteriolysis depends upon the fact that though many of the amboceptors unite with the microbes, and many of the complements with the amboceptors,

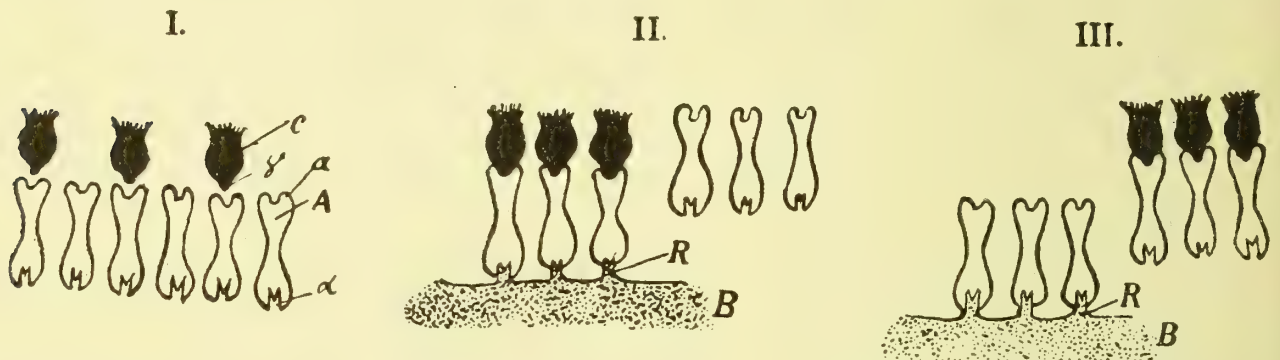


FIG. 78.—DIAGRAMMATIC REPRESENTATION MODIFIED FROM NEISSER AND WECHSBERG SHOWING DEVIATION OF COMPLEMENT.

A. Amboceptor. *a*. Complementophile group of the amboceptor. *x*. (Cyto-) bacteriophile groups of the amboceptor. *C*. Complement. *V*. Haptophore group of the complement. *B*. Bacterium. *R*. Receptors of the bacterium.

I. Serum containing pure complement and a number of free amboceptors.

II. Shows amboceptors anchored to the bacterium, and through the increased affinity thus brought about the complement also becomes anchored to the amboceptor so that the bacterium may be dissolved.

III. Deviation of the complement by superfluous amboceptors having an increased affinity for it.

it may not be with amboceptors attached to the cells, but to free amboceptors that the complements attach, so that a deviation resulting in diminished activity is brought about.

Some doubt has been thrown upon the explanation by later researches by Bordet and Gay,¹ but the fact that excess of amboceptors inhibits the bacteriolytic effect remains nevertheless.

The remedy first to suggest itself is that the patient should receive not only amboceptor serum, but also a serum rich in complements, but this is impossible, because no method has been devised by which the complement can be much increased by experimental manipulation.

One further difficulty presents itself in the practical application of such serums, and that is the fact that the amboceptor, being itself an antigen, may, when superfluous in amount and frequent in introduction in the patient's blood, lead to the formation of antiamboceptors by which its utility is further destroyed.

These are, however, theoretical considerations whose validity as objections to the employment of antimicrobial serums must give way before the results of practical experience with such serums, and must depend upon the unmixed or mixed character of the antimicrobial serums, for, as has been said, nearly all are active in more than one way.

All of the antimicrobial serums are said to lose their virtue quickly, so that they should be secured and employed as freshly as possible.

¹ Ann. de l'Inst. Pasteur, xx, June 25, 1906, No. 6, pp. 267, 298.

Antistreptococcic Serum.—This was first prepared by Marmorek.¹ Highly virulent cultures of streptococci were secured after elaborate laboratory manipulations, and were then injected in increasing doses into horses. After the horses had been carried through a long course of treatment, and finally brought to a point where they could tolerate without adverse symptoms large doses of the culture, they were given a period of rest during which the cocci all disappeared from the blood, after which they were bled, the serum separated and prepared for the market.

The serum has been extensively investigated with reference to all of the streptococcic infections—erysipelas, suppuration, puerperal fever, scarlet fever, ulcerative endocarditis, the complications of pulmonary tuberculosis, and others.

The generally prevailing opinion is that the serum is most disappointing, though numerous special cases are recorded in which good was apparently achieved. Many are convinced of its utility.

Certain theoretical objections present themselves as obstacles to exact knowledge of what the serum may do. The first of these is uncertainty of the specific identity of the streptococcus. It is commonly assumed that the organisms obtained by culture from the diseases mentioned in the list in which this serum is employed are identical, but this is by no means a certainty.

Experiments with all the reactions of immunity show them to be highly specific, so that if there were differences in the streptococci obtained from different sources, and used as antigens, they would give different results in the resulting antibodies.

Van de Velde² endeavored to overcome this difficulty by making a "polyvalent serum" by injecting the experiment animal with mixtures of streptococci from various sources.

Moser and Tavel³ endeavored to make sure that the streptococci employed in making the serum came from human beings, and were virulent for such, by inoculating the experiment animals with cultures made from patients suffering from scarlatina, etc.

A second and more cogent objection is found in the slight effect of the antigen upon the horse or other animal used to furnish the serum. A. von Lingelsheim says in his paper upon "Antistreptococcic Serum" in Kolle and Wassermann's *Pathogenie Mikroorganismen*, "The animal body is not a retort into which it is only necessary to put a poison in order after a given time to get an antidote out." In order that the antibody be produced, it is necessary that the animal be forced to *react*, which horses do not always do when injected with streptococci. The writer of this paper recalls an interesting and suggestive experience in the course of his own experiments that may be used to exemplify how mistaken one may be in the effects produced. Two horses were being subjected to immunizing experiments, one with virulent (!) streptococci, the other with pneumococci. Each injection appeared to be followed by a mild reaction. The doses were cautiously increased, and eventually

¹ Ann. de l'Inst. Pasteur, ix, No. 7, July 25, 1895, p. 593.

² Ibid., 1896; Archiv. de méd. Experimentelle, 1897, No. 4.

³ Münch. med. Wochenschrift, 1902, p. 1729; Jahr. f. Kinderheilkunde, Bd. 57, H. 1; Berl. klin. Wochenschrift, 1902, S. 13.

reached several hundred cubic centimeters, and the serums were thought about ready to be of therapeutic use. It was decided to give one more dose, the cultures were prepared, and eventually injected, when, to his consternation, the veterinary surgeon discovered that he had mistaken the cultures and given them to the wrong horses respectively. It was supposed that both horses would die, but, to the disgust of the writer, both lived, showing that the cultures, though virulent for rabbits, were practically devoid of virulence for horses, and probably incapable of exciting antibody formation upon injection.

A third source of dissatisfaction is the difficulty of testing the serum and accurately estimating its value and the absence of any recognized standard. This makes it quite probable that good and bad serums may be abroad, some giving beneficial action, others devoid of power.

Lastly, in all our considerations we must be mindful of the mixed character of the affections treated and the difficulty of drawing correct inferences from individual observations and opinions. Scarlatina and erysipelas are diseases upon whose mortality correct figures are obtainable, and in these affections the serum seems to have made little if any impression.

In the case of sepsis, suppuration, and endocarditis it is more difficult to secure accurate data, and it is upon them that the greater benefit is said to have been achieved.

It seems useless to quote from the literature in support of that which must rest so largely upon opinion as deductions upon the efficiency of this serum. It may be that the future will provide means of overcoming the difficulties mentioned, when more accurate information will be available. In summarizing, it seems only necessary to add that during the fifteen years since the first paper published by Marmorek, the serum has failed to fulfill his expectations, and has apparently lost ground instead of establishing itself as a useful remedy.

Antipneumococcic Serum.—In 1891 G. and F. Klemperer¹ showed that the blood serum of rabbits immunized against the pneumococcus was able to protect mice from fatal infection. Their endeavors to apply the principle to human therapeutics failed.

Hughes and Carter² endeavored to exert a favorable impression upon the course of pneumonia by injecting patients with the blood serum of other patients that had just passed the crisis. Some good appeared to be accomplished, but the results were contradictory and the experiments were soon discontinued.

Foa and Carbone,³ Mosney,⁴ Washbourne,⁵ Pane,⁶ McFarland and Lincoln,⁷ Lambert,⁸ and others have prepared serums by injecting whole cultures of the pneumococcus into horses, etc., and using this serum for the treatment of

¹ Berl. klin. Wochenschrift, 1891, Nos. 34 and 35.

² Therapeutic Gazette, October 15, 1892.

³ Gazz. Med. di Torino, 1891; Rif. Med., 1891.

⁴ Archiv. de méd. Exper. et d'Anat. Path., 1892.

⁵ Brit. Med. Jour., February 27, 1897, p. 510.

⁶ Centralbl. f. Bakt., etc., Mai 29, 1897, xxi, 17 and 18, p. 664.

⁷ Jour. Amer. Med. Assn., December 16, 1899, p. 1534.

⁸ Ibid., 1900, i, p. 901.

pneumonia in human beings. Nothing but disappointment followed. Each investigator believed the serums to be possessed of antimicrobial and perhaps of antitoxic properties, and those first employing the serums in treatment were pleased with the early results. After the first enthusiasm had passed and a comparison of cases treated and cases untreated by the serums was made, there was very little to be said for the serums and interest in them declined. Römer¹ believed the serum cured 80 per cent. of the cases of *ulcus serpens corneæ* in which he employed it.

These products are all subject to the same critical and theoretical objections discussed in reference to the antistreptococcic serum.

Antitubercle Serum.—Many attempts have been made to produce a favorable effect upon the progress of tuberculosis by the employment of some form of immune serum. Such serums as were supposed to be antitoxic in character have been considered above. At this point only such as are supposed to be antimicrobial in character are to be discussed. The mixed character of the serums and the artificial character of our classification must, however, be taken into account should the reader find the separation of the preparations to be imperfect.

The first attempts were made by Héricourt and Richet,² Daremberg,³ Babes and Proca,⁴ and were based upon the assumption that the dog, being naturally immune from tuberculosis, would, after a few injections, furnish a useful therapeutic serum. Babes believed that the serum prepared by himself and Proca inhibited the tuberculin reaction.

Patterson⁵ tried the serum of fowls, injected with large quantities of avian tubercle bacilli, for the immunization of rabbits and guinea-pigs, and thought that he saw favorable results.

In 1897 E. A. de Schweinitz⁶ injected cows and horses with increasing quantities of a culture of greatly attenuated tubercle bacilli, and produced a serum which seemed to give encouraging results at the hands of Trudeau, Stubbart, Richardson, and others by whom it was employed.

The serum made by Fisch⁷ by immunizing a horse to Tuberculin R should upon theoretical grounds contain bacteriologic amboceptors, and so come in the present group. It has already been mentioned as having given some good results.

The best known of the antitubercle serums is *Maragliano's serum*. Maragliano⁸ began his work quite early and has published a number of papers upon the methods employed, the theory upon which his experiments were based, and the results obtained. From a perusal of these papers it is difficult to determine exactly what his methods were. M. P. Ravenel, who went to see his work on behalf of the Henry Phipps Institute, gives the following synopsis

¹ Archiv. f. Ophthalmol., 1902.

² Compt. rendu de la Soc. di Biol., 1890, p. 630.

³ Traitement de la phthisie pulmonaire, Paris, 1892.

⁴ La méd. moderne, 1896.

⁵ Amer. Medico-Surg. Bull., January 25, 1898.

⁶ Centralbl. f. Bakt., etc., 1897, xxii, 8 and 9, September 15.

⁷ Jour. Amer. Med. Assn., October 30, 1897.

⁸ Berl. klin. Wochenschrift, 1895, No. 32.

of the method of preparation:¹ "The serum for therapeutic use is produced from horses and cows, following in general the methods employed in the production of other sera against infectious diseases—that is, a progressive active immunization of the animals, during which the defensive antibodies are produced in the blood. The methods of bringing about this immunization, and of exactly measuring the protective power of the serum of immunized animals, constitute the pith of Maragliano's discoveries. One of the great difficulties in the way of producing an antituberculous serum has always been the apparent impossibility of obtaining the sum total of the toxins formed by the tubercle bacillus. This difficulty Maragliano believes he has overcome.

"The animals to be immunized receive under the skin increasing quantities of two preparations—Liquid F. and Bacillary Pulp. The former of these consists of equal parts of Maragliano's watery tuberculin and the filtrate from living and virulent tubercle bacillus cultures, obtained by passage through the Pasteur-Chamberland filter. The bacillary pulp is made up, as the name implies, of the substance of the tubercle bacilli, unaltered by heat or other agents. It is obtained by grinding the bacilli with sand and water and subsequent passage through a Pasteur-Chamberland filter. Equal quantities of these two fluids are injected at the same operation, but in different parts of the body. If there is no marked fever and no local reaction, a second injection is given after three days, the quantity being doubled. Subsequent injections are made at intervals and in quantities depending upon the condition of the animal and its reaction to the injections, both local and general, the dose, however, being progressively increased. This process is kept up until the serum of the animal is found to have a high agglutinative power, as tested by Maragliano's methods." Ravenel continues: "It appears established that Maragliano has succeeded in producing a serum which protects experiment animals against the poisons of the tubercle bacillus, so far as we have been able to obtain them, and also against the tubercle bacillus itself in pure culture, when given in doses that do not overwhelm the animal, but which have been shown to be fatal. From the laboratory standpoint it seems that his claims cannot be successfully contested. The curative value of his serum is not so well established."

In a lecture read before the Henry Phipps Institute, Philadelphia, March 28, 1904, Maragliano says: "In these nine years there have been at least 20,000 cases of tuberculosis treated in this way" [referring to the method of employing the serum in therapeutics]. "Naturally it is impossible for me to have data upon all of these cases. I have only been able to collect the notes of 2,899 cases.

"These were reported in a statistical communication by one of my most valued coworkers, Professor Mircoli, to the Congress of Tuberculosis in Naples. These statistics show that out of more than 250 cases of circumscribed nonfebrile tuberculosis, 38 per cent. were cured and 49 per cent. were much improved; that out of 938 cases of circumscribed febrile tuberculosis, 18 per cent. were cured and 54 per cent. were improved; that out of 665 cases of diffuse tuberculous broncho-pneumonia without mixed infection, 14 per cent.

¹ Report of the Henry Phipps Institute, 1905, p. 302.

were cured and 43 per cent. were improved. Out of 332 cases of diffuse tuberculous broncho-pneumonia with mixed infection, 9 per cent. were cured and 36 per cent. improved. Of 712 cases with cavities and lesions 6 per cent. were cured and 40 per cent. improved. Of all these patients, 2,396 were in a febrile condition. The fever disappeared in 1,111 cases—that is, in 46 per cent.”

These results of Maragliano, thus tabulated by Mircoli, are most interesting and suffice to indicate that the serum should be given thorough and systematic trial. Unfortunately, those who have tried it have been so disappointed in their early results as to abandon it, perhaps prematurely, thus making it impossible to express any definite opinion upon the status of the remedy.

Antiplague Serum.—Yersin, Calmette, and Borrel¹ found that the serum of animals, immunized to killed cultures of the plague bacillus, was able to protect other animals against infection. Yersin² employed horses for this purpose, the serum being used in the treatment of human beings. Lustig³ prepared a serum by injecting animals with a nucleoproteid extracted from cultures of the plague bacillus. Laboratory experiments showed that the serum of Yersin was both antimicrobial and antitoxic, that of Lustig chiefly antitoxic.

Tavel⁴ also prepared a serum upon the same general lines as that of Yersin.

The doses of these serums must be very large—100 to 300 c.c.—and the best results follow intravenous administration. The statistical studies given by Yersin from its use in Amoy,⁵ in Nhatrang (Annam),⁶ and by Calmette and Salimbeni⁷ give excellent evidences of the value of the serum. Thus the latter authors, who used the serum at Oporto, report 142 cases treated, of whom 24 died, the mortality being 14.78 per cent.; at the same time 72 patients were not treated and 46 died, the mortality being 63.72 per cent. The serum effects an immediate amelioration of the pain in the buboes, limits the inflammatory process, and frequently aborts the suppuration.

Cairns,⁸ who used the serum at Glasgow, concluded that it was of the greatest value.

Antityphoid Serum.—Chantemesse,⁹ Pope,¹⁰ Steele,¹¹ and Bokenham¹² all prepared serums by injecting large animals with killed cultures of the typhoid bacillus. Macfayden¹³ endeavored to improve the method by freezing cultures with liquid air and then grinding them so as to liberate the intracellular toxins. After melting, the products were injected into horses.

None of these serums has survived more than a few trials, and the only

¹ Ann. de l'Inst. Pasteur, ix, 1895.

² Ibid., xi, 1897.

³ Siero-therapia e vaccinaz, prevent. contro la peste, Turin, 1899.

⁴ See paper by Krumbein and Glücksmann, Centralbl. f. Bakt., etc., xxx, 1901; Zeitschrift für Hygiene, xl, 1902.

⁵ Ann. de l'Inst. Pasteur, 1897, p. 81.

⁶ Ibid., 1899, p. 251.

⁷ Ibid., p. 865.

⁸ Lancet, 1903, i, p. 287.

⁹ Gaz. des Hôpitaux, 1898, lxxi, p. 397.

¹⁰ Brit. Med. Jour., 1897, i, p. 259.

¹¹ Ibid., i, 1897.

¹² Trans. Path. Soc. of London, 1898, p. 373.

¹³ Brit. Med. Jour., 1903, April 3.

one that is still in the public mind is that of Chantemesse, prepared with a typhoid toxin, which is discussed under the antitoxic serums.

Antidysenteric Serum.—Shiga, the discoverer of the dysentery bacillus, was the first to experiment with the effects of the immune serums. He¹ and Kruse² both found, as have many others since, that the serum of patients and, far more, the serums of animals immunized by the injection of cultures of the bacillus, contained agglutinative and bactericidal substances.

Shiga³ was the first to employ the immune serum in practice in an epidemic of dysentery in Japan. In this epidemic 22 per cent. of the infected persons died. Three hundred patients were treated with the serum in the hospital of Tokio, the death rate among these being 7 per cent. In all of these cases the duration of the disease was much shortened. Kruse was able to substantiate the validity of Shiga's claims.

Rosenthal and Gabritschewski⁴ made and employed a similar serum to that of Shiga in 157 cases of dysentery, and found that they were able to reduce the mortality from 11 to 4.5 per cent. by its use.

There can, therefore, be no doubt of the value of this serum, though the fact that there are several different strains of the bacilli, with individual peculiarities, makes some theoretical probability that any one serum may not give uniform results in practice.

Antigonococcic Serum.—Christmas,⁵ by artificial cultivation of gonococci, secured a toxic substance precipitable with ammonium sulphate. By injecting this into rabbits he obtained an antitoxin that neutralized the poison *in vitro*. The serum was not used in man.

Torrey⁶ secured rich cultures of gonococci in a medium consisting of beef-infusion peptone broth rendered slightly acid, and receiving an addition of an equal part of ascitic fluid. After pouring the broth and ascitic fluid together, the mixture is heated to 60° C. for several hours, then set aside in the thermostat for twenty-four hours to test the sterility.

The cocci are cultivated at 36 to 37° C., and after about six days thoroughly cloud the medium when it is gently shaken. With such rich cultures rabbits are intraperitoneally injected with doses of 10 c.c. every five or six days until six doses have been given. Each dose is followed by a marked reaction, and if the immunization is pushed, the rabbits become cachectic and die. Each rabbit will furnish a total of 70 to 90 c.c. of the serum. Rogers⁷ used this serum in the treatment of gonorrheal infection of the joints with what appears to be extraordinary success.

Antimeningococcic Serum.—The first antimeningococcic serum seems to have been prepared by Bonhoff,⁸ and to have been employed for prophylaxis only. Von Lingelsheim⁹ prepared a serum by injecting dead and living me-

¹ Centralbl. f. Bakt., etc., 1898, xxiii, Heft. 14.

² Deutsche med. Woch., 1900, No. 40; 1901, Nos. 23 and 24.

³ Ibid., 1901, Nos. 43, 45; 1903, No. 7.

⁴ Centralbl. f. Bakt., etc., Ref. Bd. xxxiv, 1904, ii, 16, 17.

⁵ Ann. de l'Inst. Pasteur, 1900, p. 331.

⁶ Jour. Amer. Med. Assn., 1906, xlv, p. 261, January 27.

⁷ Ibid.

⁸ Münch. med. Woch., 1901, xlviii, S. 89.

⁹ Klin. Jahrbuch., 1906, Bd. xv, Heft. 2.

ningococci into the subcutaneous tissue of a goat. The difficulty of properly testing the merits of this serum upon animals seemed an insuperable obstacle to its employment. Kolle and Wassermann¹ experimented extensively with antimeningococcic serum and developed methods for determining its mode of action and its activity. Jachmann² experimented with a serum, prepared by Merck at the Darmstadt works, according to the method of Kolle and Wassermann, and suggested its employment by the intraspinal method. Before injecting 20 c.c. of the serum, the cerebrospinal fluid was permitted to escape in quantities varying from 20 to 50 c.c.

Flexner and Jobling³ have undoubtedly had the best success with a serum first prepared with goats and subsequently with horses, into which whole cultures of the meningococcus are injected.

Churchill⁴ gives an excellent statistical study of Flexner's results upon 600 cases treated with the serum, with a mortality of about 25 per cent.—the death rate in cases not treated being 75 to 80 per cent.

Flexner⁵ gives the following tabulation of 712 cases of the disease in which a bacteriologic diagnosis was made and the serum used:

Age, Years.	Total Number of Cases.	Recovered.	Died.	Mortality.
1-2.....	104	60	44	42.3%
2-5.....	112	82	30	26.7%
5-10.....	113	95	18	15.9%
10-15.....	101	73	28	27.7%
15-20.....	107	72	35	32.7%
20 +.....	175	106	69	39.4%
Total of all ages.....	712	488	224	31.4%

The serum therefore shows itself to be a most important addition to the therapeusis of a disease for which we were unable to do anything in the past.

The serum is found to be effective only in those cases of cerebrospinal fever that are due to infection with the diplococcus intracellularis. It is of no value in the tuberculous varieties nor those due to the pneumococcus or streptococcus. Flexner's serum is purely specific. For this reason it is necessary to know that the patient about to be treated is suffering from the variety of cerebrospinal meningitis due to Weichselbaum's diplococcus intracellularis.

To obtain this surety is not difficult, for it is essential in the employment of the remedy to do a lumbar puncture so as to introduce the serum directly into the spinal canal. The method of performing lumbar puncture is familiar and is elaborately detailed in the article by Quinke in the volume of this series on Diseases of the Nervous System.

Technic of Administration of the Serum.—Lumbar puncture is performed naturally under strict antiseptic precautions and according to the rules laid

¹ Deutsche med. Wochenschrift, 1906, No. 16.

² Ibid., No. 20.

³ Jour. Exper. Med., 1907, ix, p. 168; 1908, x, p. 141.

⁴ Jour. Amer. Med. Assn., 1909, liii, No. 2, p. 841.

⁵ Ibid., October 30, 1909, p. 1443.

down by Quincke. The pressure of the cerebrospinal fluid should be noted by counting the drops that flow per minute, or better, by the sphygmomanometer. The color and possible turbidity are noted during the operation. On a glass slide a few drops are immediately collected, stained, and examined. Tubes containing culture media, agar, or blood serum, may also be inoculated for later examination. In a positive growth transparent colonies running together and forming a thin layer are noted. The smears may be employed for diagnosis equally as well as the cultures. The growth is stained according to Gram.

It is well to obtain from 30 to 45 c.c. of spinal fluid if possible. Through the same needle, still present in the spinal canal, an equal quantity of curative serum to that which has been removed by lumbar puncture is *slowly* injected, *at once* if the lumbar fluid is at all turbid, even before the microscopic examination has been completed.

The method is not difficult and is easily performed by those familiar with the operation of lumbar puncture. Naturally the results in hospital management have been more favorable than those in private practice, due to the greater facilities at hand in the institution. Lumbar puncture requires some skill and must be carefully carried out. The lack of experience in the family practitioner is responsible for some of the failures.

An essential to the success of the treatment is the early administration of the serum by lumbar puncture. This is the only method at present; the subcutaneous use is absolutely ineffective. The serum should be injected in doses of not less than 30 c.c. whenever at all possible. In severe and fulminant cases larger doses must be used and repeated in 12 hours. It is necessary to administer the serum until the spinal fluid of the patient has again become sterile. A relapse is treated just as the original attack. Chronic cases and those treated late are much more resistant.

The effect of the serum reveals itself by a rapid fall in temperature, general amelioration of the severe symptoms (particularly the headache), a briefer course of the disease, and an absence of sequels. In some instances the early employment of the serum has aborted the attack. Many of the complications of the malady, such as the arthritis, are relieved by the local (subcutaneous) use of the serum.

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